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THE USE OF REFRIGERATION IN AMPUTATIONS AND PERIPHERAL VASCULAR DISEASE*

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BOSTON

DURING the last three and a half years, an attempt has been made at the Boston City Hospital to evaluate the role of reduced temperatures in the treatment of various types of peripheral vascular disease. Particular interest has been directed toward the employment of refrigeration as an anesthetic agent in amputations of the extremities for gangrene due to primary arterial disease. In addition, the effects of localized chilling of tissues in states of impending ischemia, due to sudden arterial occlusion, sepsis and venous thrombosis, have been observed.

The use of cold as a therapeutic agent is not new. Ice applications and cold compresses for the relief of pain and reduction of inflammation are as old as medicine. Within recent years, newer concepts of refrigeration have been developed. The familiar work of Fay and his associates in reducing temperatures over long periods of time in patients suffering from cancer emphasized that a lowered metabolic state, comparable to hibernation in lower animals, is possible in human beings. Whatever the value of these studies so far as any positive attack on the broad field of malignancy is concerned, they pointedly demonstrate that tissue metabolism can be slowed to a degree hitherto not thought possible. A more recent development, and the one that this paper is particularly concerned in describing, has been prompted by the observations of Allen[1] on the use of refrigeration in diabetic or arteriosclerotic gangrene or both.

Experimental Evidence

There is ample evidence that when the extremities of animals become totally ischemic as the result of the deprivation of blood supply by a tourniquet, exposure to room temperature or to an increased temperature results in rapidly progressive tissue necrosis. It has further been observed that the reduction of temperature enables limbs to survive for a much longer period of time. Brooks and Duncan,[2] for example, noted that a rat's tail became gangrenous within four hours after ligation at a temperature of 40°C. When, however, the temperature was reduced to approximately 4°C., the survival period was extended to as long as four days. Allen[3] observed that the hind legs of rabbits, cats and dogs survive asphyxia for thirteen to fifteen hours at room temperature. When the temperature is reduced and maintained at approximately 2 to 4°C., the dangers of ligation are greatly diminished. Under these conditions, limbs showed a survival period of fifty hours or longer. Furthermore, the phenomena of shock, thrombosis, infection and injury to blood vessels and nerves were markedly inhibited.

Clinical Considerations

The results of animal experimentation obviously suggest imitation in human beings. It thus appears that the use of ice as an anesthetic agent might be of particular value in a group of poor-risk patients, in whom mortality in major amputations has always been appallingly high. The type of patient found in the clinics of municipal institutions — undernourished, neglected, discouraged, often with an advanced state of peripheral arterial insufficiency, seen for the first time with rapidly spreading gangrene and sepsis, and with histories of previous cardiac and cerebral accidents — immediately suggests the likeliest candidates for this form of therapy. In these patients, spinal or general anesthesia, with additional operative shock, are all too frequently the factors militating against recovery. On the other hand, it is probable that, except in rare cases, the method of refrigeration has little to offer in groups of selected patients watched carefully by organized groups of physicians and surgeons. In these cases, anesthesia probably seldom contributes to mortality.

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Tourniquet and Refrigeration

The method under discussion, as has been stated above, is essentially one of combined ligation by means of the tourniquet and refrigeration. The application of the tourniquet itself is of considerable importance. Rubber tubing, 10 to 12 mm. in diameter, is the best material for ligation. Allen[1] has demonstrated that wide bands, such as an Esmarch bandage, by traumatizing wide masses of tissue, contribute to a greater degree of secondary shock than do narrow bands. Two turns of the tourniquet are made at the selected site, and the tubing is held in place by a clamp or knot, care being taken that the skin is not pinched. The tourniquet is applied as tightly as possible. As a preliminary measure, several ice bags are placed at the ligation level for a few minutes, in order to minimize any discomfort incidental to the placing of the rubber tubing. Refrigeration is immediately begun.

In the case of a low thigh amputation (Fig. 1), the entire leg and thigh up to the tourniquet site are surrounded by cracked ice encased in rubber sheeting or in a special container* built for the purpose (Fig. 2). A skin temperature maintained at about 8 to 10°C. has been found most desirable, assuring that the part is chilled and not frozen (Fig. 3). It must be emphasized that refrigeration is not freezing, and the terms should not be confused. Tests by an ordinary house or laboratory thermometer, held against the skin from time to time, will enable the leg to be kept at the proper temperature level.

In the average case, in our experience, it takes between two and two and a half hours to produce sufficient anesthesia to allow a painless amputation. In a thin, emaciated, arteriosclerotic limb, anesthesia is necessarily attained more quickly than in the extremity of a young, muscular patient who requires an amputation because of trauma.

No attempt should be made to hasten a refrigeration amputation for fear of too long constriction of the limb by a tourniquet. In several of our cases the tourniquet has remained on for ten to twelve hours, and in no case has there been any interference with subsequent primary wound healing of the stump. The usual criticism of undue trauma to blood vessels from a tourniquet does not appear to be warranted under conditions of refrigeration. Moreover, in certain cases we have intentionally waited longer than the customary anesthesia period in order that the patient's general condition might improve. It has been apparent that reduced temperatures have definitely promoted the comfort of the patient.

As a rule, little if any preliminary medication is needed, unless the patient is apprehensive or nervous. Indeed, the improvement of the mental and physical state after refrigeration has been initiated is dramatic.

FIGURE 1. *Leg from Tourniquet to Toes Encased in Cracked Ice and Surrounded by Rubber Sheeting.*
The lower leg and foot are exposed for demonstration purposes.

Operation and Aftercare

When the desired anesthesia has been reached, the patient is moved, with the ice container, to the

*This container was designed by Dr. Andrew Webster, intern on the Third Surgical Service, Boston City Hospital, who has assisted in this study. The Therm-O-Rite Products Company, Buffalo, New York, has developed an electrically operated, thermostatically controlled refrigeration unit that does away with the obvious difficulties associated with ordinary refrigeration methods.

operating room and placed on the table. The container is removed and the limb is prepared for operation. The incision is made 10 to 15 cm. below the level of the tourniquet (Fig. 4). The type of amputation should be the simplest. Our preference is for a circular amputation, with staggering of skin, muscle and bone layers and without the formation of flaps, leaving the skin incision dog eared on each side. This method assures a comfortable and ultimately a good-looking stump. No drains are ever used (Fig. 5). The omission of drainage is as essential to primary healing in the refrigerated stump as it is in elective amputations done under any of the commoner methods of anesthesia.

It is our conviction that the guillotine amputation with no attempt at closure is preferable to the employment of drains and that in the presence of rapidly ascending infection it is the procedure of election. The tourniquet is released just prior to closure of the wound. Circulation returns promptly, and there is bleeding in proportion to the vascular supply of the limb. It will be observed that there is no thrombosis within the blood vessels and that the blood is in its normal fluid state. The muscle bundles appear healthy and a somewhat brighter red than usual, comparable to the color of meat subjected to icebox temperature.

In this series of cases, the traditional amputation sites have been adhered to fairly closely. It has been suggested,[4] however, and, we believe, with merit, that lower amputation levels in the leg may be selected. Despite the minimal circulation present in arteriosclerotic extremities, refrigeration, by reducing tissue metabolism and lessening the demands on the available blood supply, permits removal of a limb at a lower limit than ever before thought practical — for example, 5 to 7 cm. above the ankle. Since the saving of life and not the correct fitting of a prosthetic appliance is the purpose in many older patients, this procedure is a reasonable one. It is recommended in selected cases.

Patients undergo refrigeration amputations without pain and without shock. Pulse and blood-pressure levels are not changed by the operative procedure. The usual postoperative discomforts — nausea, vomiting, and pain — are not experienced. The following case reports illustrate these facts.

Case Reports

Case 1. S. G., a 10-year-old boy, suffered a compound fracture of both bones of the left forearm on October 4, 1941, when he fell while playing in a stable. He was operated on shortly after admission to the hospital. The usual procedure of treating compound fractures was assiduously carried out, including wound débridement, introduction of sulfanilamide powder into the wound and prophylactic tetanus-gas gangrene antitoxin. Three days later, the temperature was 104.2°F. and the pulse 170 (Fig. 6). The wound was inspected and the arm was found to be swollen, with no pulse at the wrist and crepitation of the tissues. A diagnosis of gas-bacillus infection was made. The wound and adjacent soft tissues were opened widely, irrigations of hydrogen peroxide were instituted, and therapeutic doses of gas-gangrene antitoxin (10,000 units every 4 hours) x-ray and sulfanilamide were given. Despite all treatment, the infection rapidly spread upward and the arm became gangrenous. Permission for amputation was refused by the patient's parents. Four days later, he was practically moribund, with a rectal temperature of 103°F., a pulse of 160 and an extension of the infection into the axilla and anterior chest wall. Consent for amputation was finally obtained.

A tourniquet was applied to the upper arm just above the grossly sloughing area, and the extremity below the tourniquet was packed in ice. Within 2 hours, the patient's condition improved remarkably. He became brighter and less toxic appearing, and showed a drop in temperature and pulse rate. Because of this slight improvement, amputation was delayed for approximately 20 hours more, in the hope

Figure 2: *Home-Made Wooden Container.*
This box is much easier to handle than rubber sheeting.

that further improvement would enhance the chances of recovery (Fig. 7). At that time a quick guillotine high-arm amputation was done in the patient's bed. He stood the operative procedure well. Convalescence was entirely uneventful, and he was discharged home in 3 weeks.

The refrigeration amputation was probably not the only factor in this patient's recovery. It seems certain, however, that had any other anesthetic agent been used he would not have survived.

CASE 2. J. B., a 71-year-old man, was admitted to the hospital on July 26, 1941, with a diagnosis of fracture of the left patella. Five days later, under spinal anesthesia, an open reduction was performed with silk-suture technic. Six days later, sepsis in the wound was observed and drainage was instituted. Improvement occurred for a time, but sepsis then progressed, and wide incision and exploration were done, again under spinal anesthesia, on November 17.

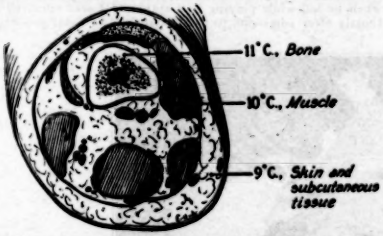

FIGURE 3. *Temperatures Taken at Skin, Muscle and Bone Levels in the Amputated Stump following Refrigeration.*

This figure demonstrates that cold penetrates to sufficient depth within two or three hours to ensure adequate anesthesia for amputation.

Necrotic fragments of the patella were removed and it was noted that the joint cartilage was completely destroyed. X-ray films showed destruction of the upper end of the tibia and the lower end of the femur. The patient ran a stormy postoperative course, including pneumonia at the bases of both lungs, and continued to run a spiking temperature between 101 and 103°F. He went downhill rapidly, and a refrigeration amputation of the thigh was decided on. After 4 hours of refrigeration, the patient's condition did not improve and death seemed imminent. Amputation was postponed. After another interval of 3 hours (7 hours of refrigeration), his condition seemed favorable enough to warrant operation.

Thigh amputation was done painlessly and without any perceptible change in the pulse or blood pressure. The stump was left open and traction sutures were applied to the skin. The postoperative course was uncomplicated. No further plastic procedure was necessary on the stump, and the patient left the hospital in 6 weeks.

This case is typical of the old, bad-risk patients who, because of sepsis and arterial insufficiency, withstand poorly major operative procedures on the extremities.

Postoperative management is predicated on the principle that temperatures may be reduced or elevated according to the patient's needs. The temperature of the stump is allowed to return to normal by the gradual withdrawal of the ice bags placed about the stump. If, on the other hand, there is any tendency to sloughing or infection of wound edges, further reduction of tissue metabolism to a level for which the existing blood supply is adequate should be initiated.

Healing

Most wounds from refrigeration amputation when tightly closed heal per primam, and the percentage of first-intention healings is comparable to that after similar operations done under other anesthetics. It is to be emphasized, however, that refrigerated incisions heal more slowly than others, because of the known tendency of cold to inhibit agglutination of wound surfaces. Sutures should therefore not be removed from wounds for fifteen to twenty days. Raising the temperature of the stump as rapidly as possible promotes rapid healing, but this is not justifiable because of the risk of incurring sloughs. Slow healing is better than no healing at all.

Clinical Data

In the ten-year period from 1930–1939, there were at the Boston City Hospital 162 cases of major gangrene of the extremities from different causes that were deemed inoperable, either because of the spread of the disease itself or because of other factors, such as old age and cardiorenal, cerebral or other complications (Table 1). The mortality rate was 100 per cent. It was believed that if a certain percentage of lives could be salvaged from a comparable group of bad-risk patients, the refrigeration method would be decidedly worth while. In addition, the mortality rate on 270 cases of major gangrene operated on at this hospital between 1930 and 1939 was 53 per cent. Although no attempt is made here to analyze this high mortality figure, and although it is certain that many poor-risk cases were included in the group, it is our conviction that it is excessively high.

Fifty-four patients were refrigerated. Of these, 50 came to amputation and 4 died before operation. The latter were moribund on entry. The ages

TABLE 1. *Results in Cases of Major Gangrene, with and without Amputation and with and without Refrigeration.*

TYPE OF CASE	NO. OF CASES	NO. OF DEATHS	PERCENTAGE MORTALITY
Unoperated cases, with complications (1930–1939)	162	162	100
Operated cases, with and without complications (1930–1939)	270	142	53
Unoperated cases, with refrigeration (1940–1943)	4	4	100
Operated cases, with refrigeration (1940–1943)	50	16	32

ranged from fifty to ninety, with 1 patient in the second decade, 8 in the sixth, 17 in the seventh, 24 in the eighth and 4 in the ninth. Forty-nine patients suffered from advanced arteriosclerotic gangrene, with complications of diabetes and sepsis (16 cases), recent cerebral accidents and cardiac failure (25 cases) or other serious infirmities.

The immediate salutary effect of chilling of tissues on the more prominent signs and symptoms was most striking. Relief of pain was observed in every case and without the aid of the customary medica-

tion. It is well known that sudden arterial occlusions, as from embolism, are most painful and that great discomfort persists for many hours after the initial obstruction. It has been in this group that the relief of pain has been most dramatic. Shock has always been an outstanding and disturbing feature of thigh amputations, both during and after operation. In addition to operative trauma, general and spinal anesthesia, particularly the latter with its frequent attendant fall in blood pressure, contribute greatly to secondary surgical shock. This phenomenon is not observed in refrigeration operations.

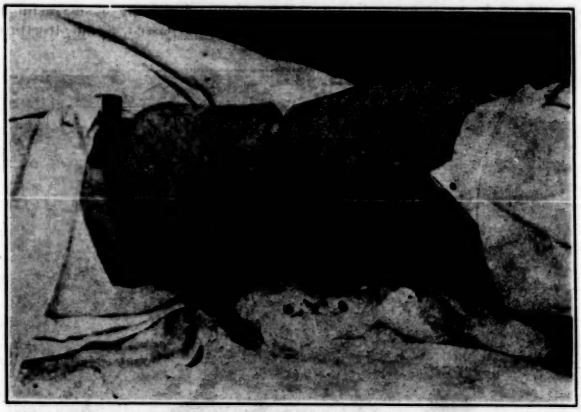

FIGURE 4. *Simple Circular Amputation below the Tourniquet Site.*
The tourniquet remains on during operation and is removed just before closure of the fascia.

There was little if any pulse or blood-pressure change in this series; in fact, shock was practically absent in 50 cases. The progress of gangrene and sepsis was notably inhibited in 48 cases by the application of cold. In several of these cases a tourniquet and refrigeration were applied for as long as twelve hours without progress of infection or gangrene and with first-intention healing following amputation. At first, doubt was entertained as to the effects of low temperatures on wound healing and breaking down of the operative site was expected. For this reason, the first few amputations, because of gangrene and sepsis, were done by the guillotine method, with secondary closure performed later. Subsequently, all wounds were tightly closed except those in which there was an unusual amount of rapidly ascending infection.

In 50 cases of amputation, there were 16 deaths, a mortality of 32 per cent (Table 1), and a salvage, in terms of 1930–1939 figures for unoperated cases, of 68 per cent. In addition, by this method there has been a reduction of 21 per cent in mortality from the figure of 53 per cent on operated cases during the ten-year period 1930–1939. In a series of 50 unselected cases in another municipal hospital, Crossman et al.,[5] have shown a mortality of 13 per cent under the refrigeration method, with only 1 death in the last 30 cases, a mortality of only 3 per cent. It may be pertinent to apply the tourniquet-refrigeration method as a routine procedure in all cases coming to major amputation in large municipal institutions.

The causes of death in this series are interesting, since most of the fatalities occurred after the patients were over the effects of their operation, with stumps adequately healed, and were sitting up or out of bed or ready to be discharged.

Two patients died from gas-bacillus infection in the stump. These were among the early patients refrigerated and represented consecutive cases from the same ward. They had not been given preliminary anti-gas-bacillus serum. At the present time, not only does every case get prophylactic polyvalent anti-gas-bacillus serum, but sulfanilamide is put in the wound before closure. The other 14 deaths were due to various manifestations of cerebrovascular accidents, sudden cardiac failure or pulmonary embolism.

Despite the lack of apparent relation to the anesthetic agent, these deaths must statistically be held against the operative procedure.

In a more recent study of 33 consecutive cases of major gangrene at the Boston City Hospital, taken as they came to the surgical services, including both good and bad risks, there was a total of 4 deaths, a mortality of 12 per cent — a decided contrast, al-

though in a much smaller series, to the 1930–1939 mortality rate of 52 per cent.

Refrigeration without Amputation

Local chilling of tissues without application of the tourniquet was attempted in a series of cases in which there was some factor of circulatory insufficiency that had not progressed to the point where loss of the limb was indicated. The method used was either the application of ice bags or immersion of the limb in crushed ice for several hours. It was hoped that the lowered oxygen demands of the part thus affected might avert impending gangrene, inhibit sepsis or retard thrombosis. This series is too small for the results to be convincing, but it nevertheless suggests certain important trends in the therapy of these conditions.

In some of these cases, the results were extremely gratifying; in others, they were frankly disappointing. On the encouraging side was a moderately advanced case of scleroderma, with deep infection of the fascial space in the hand. The employment of hot compresses and hot soaks resulted in a rapid spread of sepsis, with marked bleb formation. Since a state of deficient blood volume in the sclerodermic extremity was being dealt with, it became evident that increased oxygen demands engendered by the application of heat were causing a progressive spread of infection. A reduction in temperature, by burying the forearm and hand in ice and alternating this procedure with ice bags, produced a gradual but definite recovery.

This case suggested the application of reduced temperature to all extremities in which there were progressive occlusion of the peripheral arterial trunks and signs of imminent gangrene. At the present time, all cases of arterial insufficiency in the extremities, from whatever cause, are treated by the application of cold, and no longer by the old, familiar heat cradle encasing the time-honored 50-watt bulb, which so often resulted in the rapid spread of the gangrenous process. In this group may be mentioned vascular insufficiency brought about by arterial thrombosis or sudden arterial occlusion due to emboli, in which the time interval of four to five hours for doing a successful arterial embolectomy has passed, and frostbite of whatever severity. In this connection the emphasis that has been put by Webster, Woolhouse and Johnston[6] on the effect of reduced temperature in the treatment of immersion foot deserves mention. These observers noted a tremendous tissue reaction when patients suffering from immersion feet were exposed to ordinary room temperatures. There was edema, ecchymosis and bleb formation of the skin, suggestive of the reaction of feet with impaired blood supply that are developing gangrene. Reduction of temperature to 6°C. below normal skin temperature by the application of ice bags was the best single therapeutic measure used in combating this condition.

In the presence of frank gangrene of the extremities, with or without sepsis, refrigeration definitely retards the progress of gangrene and infection. In no cases in our experience, however, has

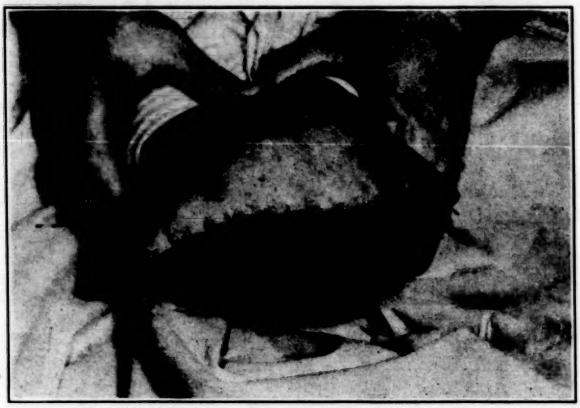

FIGURE 5. *Wound Closed without Drainage.*
The sutures should remain in place for fifteen to twenty days because of delay in wound healing due to cold.

reduction of temperature averted amputation when devitalization of a part had once occurred. It has been interesting to observe that when gangrenous limbs are exposed to ordinary room temperatures after refrigeration, gangrene progresses rapidly. A return to decreased temperature slows the process.

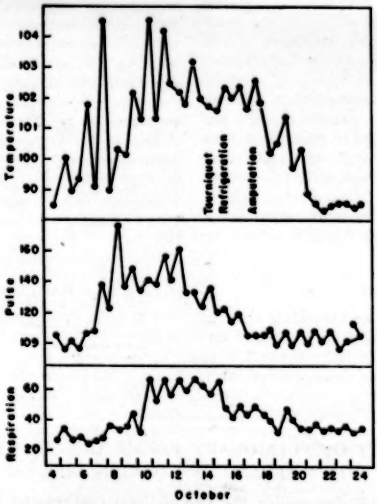

FIGURE 6. *Chart Showing Rapid Improvement after Refrigeration and Amputation.*

Several patients with deep venous thrombosis of the lower extremities, all candidates for ligation and division of the femoral vein, according to the usual requirements for such a procedure, were treated by local chilling of the tissues. All improved without further treatment. This observation is not par-

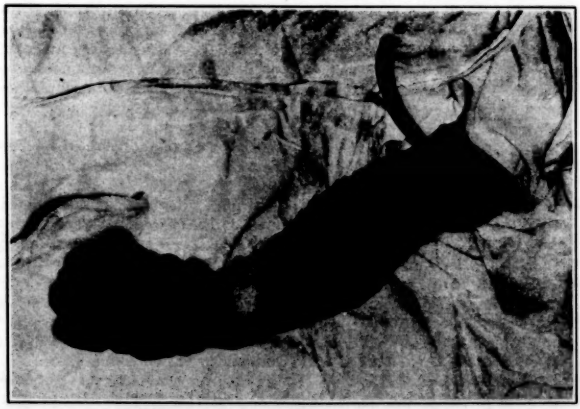

FIGURE 7. *Appearance of Arm Prior to Operation. Infection had spread beyond the tourniquet to the anterior chest wall.*

ticularly convincing, since many such cases improve with rest alone. It may be of value, however, in suggesting that prolonged cold, without freezing, inhibits thrombosis. Our preference in the treatment of deep venous thrombosis, we hasten to add, is still for interruption of the proper deep venous channels.

Refrigeration has been suggested as a valuable adjunct to the treatment of various injuries and burns. The advantages of cold in preventing toxic absorption, inhibiting bacterial growth and reducing pain, shock and edema seem to make this method desirable in traumatic cases. Its influence in military surgery, particularly under conditions of active warfare, appears to be of inestimable value. Its application is strongly urged.

Summary and Conclusions

The use of refrigeration as an anesthetic agent in major amputations of the extremities is a sound surgical procedure. It is particularly applicable to poor-risk cases, since it inhibits shock, relieves pain, retards infection and thrombosis.

A series of 50 bad-risk patients treated by the tourniquet-refrigeration method showed a marked reduction in mortality under that of a comparable series either untreated or treated by some other method. A later series of 33 patients, both good and bad risks, showed a marked reduction in mortality after refrigeration amputation.

Further possibilities in the use of reduced temperatures in the treatment of peripheral vascular disease and of injuries and in military surgery have been discussed.

I am indebted to Dr. George Miller, resident surgeon on the Third Surgical Service, Boston City Hospital, for his assistance in compiling the data used in the preparation of this paper.

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THE TREATMENT OF PULMONARY EDEMA DUE TO GAS POISONING IN WAR AND IN CIVILIAN LIFE*

With Special Reference to the Use of Positive-Pressure Respiration

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THE purpose of this paper is to outline a tentative program of treatment for patients who develop edema of the lungs following exposure to irritant gases.

For the most part, pulmonary irritants are considered acid gases, since they owe their physiologic effect to the fact that they are acids or behave like acids under the conditions of their use. They include hydrogen chloride, bromide and fluoride, chlorine, fluorine, bromine, sulfur dioxide and certain oxides of nitrogen, as well as phosgene, di-phosgene and chloropicrin. There are other less common pulmonary irritants such as ammonia and formaldehyde. The carbonyls are also included in this group because of their property of depositing finely divided particles of metal in lung tissue, thus inducing an intense pulmonary irritation and edema. The properties of these substances determine their behavior in the body. Thus, their solubility in water is a determining factor in the location of their action. Highly soluble gases, such as chlorine, ammonia and sulfur dioxide, exert their primary effects on the upper-respiratory tract and, if exposure has taken place to low concentrations or for not too long a time, the damage may be confined almost entirely to the nose and throat. Exposure to higher concentrations or for a longer period of time results in characteristic edema of the lungs, without extensive necrosis of the upper respiratory tract. The chief injury associated with inhalation of phosgene is apt to be in the lungs, in which congestion and widespread edema ultimately develop.

Chlorine and phosgene are sometimes employed as war gases for their destructive effect, but they also have been known to cause pulmonary edema in civil life as the result of disasters or industrial accidents. For example, when carbon tetrachloride (Pyrene) is used in fire extinguishers in enclosed spaces, it may be sprayed on hot metal, with a resultant liberation of phosgene. Edema of the lungs may thus take place if the concentration of the phosgene evolved is such as to cause damage to the lining of the respiratory passages as well as to the pulmonary epithelium.

Phosgene is a colorless gas at temperatures above 8°C., with an odor of musty hay. It is soluble in water, and hydrolyzes to hydrochloric acid and carbon dioxide. Since there is little immediate irritation to the larynx and trachea, the gas may reach the lungs in high concentrations. Thrombosis of the blood vessels, concentration of blood in the pul-

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monary capillaries, edema in the alveoli and in the alveolar septa and rupture of the alveoli constitute the main pathologic effects. If the patient survives the pulmonary edema, bronchopneumonia frequently follows and may be the cause of death.

In general, the pathologic condition found after inhalation of irritating gases is that of intense congestion and inflammatory edema, followed by a cellular exudate, with a varying amount of necrosis of the lining membrane of the respiratory passage. If death does not take place, there may be organization of the exudate within the alveoli and bronchi, with the production of bronchiectasis, pulmonary fibrosis and perhaps chronic suppurative lesions. The variations in pathologic effects exercised by the several gases have been fully described by Winternitz and his associates[1-5]; Haggard[6] and Henderson and Haggard[7] have pointed out the similarity in toxicologic action of all the respiratory irritants and have stressed the difference in symptomatology as due to the location of their action and the relative solubility of the irritating gases. A gas that is highly soluble in water is readily taken out of the inspired air by contact with the first moist tissue it reaches, and therefore the upper respiratory tract bears the brunt of action. On the other hand, a gas with a low solubility in water is slower to liberate its irritant principle, and the most important damage usually takes place in the pulmonary epithelium. Carlisle[8] has listed the following gases that have resulted in pulmonary edema in the course of industrial accidents: the oxides of nitrogen, phosphorus oxychloride, phosphorus pentachloride, phosphorus thiolchloride, methyl bromide, chlorine, cadmium and dust from certain alkaloids.

Sulfur dioxide is an effective refrigerant but is a respiratory irritant that has been said by Hamilton,[9] Norris and Landis,[10] Gordon[11] and Kehoe et al.[12] to be the cause of deleterious effects, although no lasting harm after exposure was observed by McCord.[13]

The symptoms depend on the solubility of the gas, as mentioned above. In some cases cough and tightness and pain in the chest are followed by shortness of breath and expectoration of seromucus, such as after exposure to the fumes of chlorine, nitric acid, ammonia and chlorpicrin. In other cases, such as after exposure to phosgene, the patient may reveal no symptoms for two to four hours except watering of the eyes and catching of the breath. Later, tightness of the chest, painful coughing and the characteristic symptoms of edema of the lungs may manifest themselves, with moist rales and bloody or frothy sputum. If the concentration of phosgene is moderately high, symptoms of pain in the chest and coughing may assert themselves soon after exposure.

Kehoe[14] has mentioned four types of effect of exposure to irritant gases. The effect of exposure to extremely high concentrations may be immediate death from anoxia due to direct damage to the respiratory membranes, rendering them impermeable to normal respiratory gases. Rapid absorption of the poison may be the chief factor in death by producing circulatory collapse (vagus shock). Differing only in degree from the above is an exposure to a high concentration of an irritant gas that results in extensive damage to the pulmonary and upper respiratory tissues, including acute hyperemia, and destruction of tissue (coagulative necrosis). If death does not take place promptly, acute emphysema of the lungs, with general acute interstitial edema, ischemia and coagulation necrosis, may result, with death the ultimate outcome. The moderate nature of a pulmonary injury makes possible an opportunity for survival. Irritative effects in the upper respiratory tract and acute pulmonary edema may be present, with threatened asphyxia or later complications, such as bronchopneumonia. Lastly, mild exposure to respiratory irritants for comparatively short periods may result in injury mostly limited to irritation of the eyes and upper respiratory tract, with redness and lacrimation, coughing, sore throat, huskiness, loss of the voice, nosebleed, moderate chest pain and excessive coughing. Recovery may take place with little or no treatment, but in some cases the condition progresses to such an extent that the patient is placed in the category described above.

Since this discussion is confined to the treatment of pulmonary edema, the chronic effect of gas poisoning and the manifestations of chronic gas poisoning will not be considered. The nature and severity of edema of the lungs after exposure to gas poisoning is difficult to predict, since the pathologic condition is subject to considerable variations depending on the gas concerned as well as on its concentration and the length of exposure. The onset of pulmonary edema may be prompt, or it may be delayed for as long as twelve hours. In the upper respiratory tract an inflammatory reaction may take place with a serosanguineous discharge; later, ulceration and hemorrhage may manifest themselves. In certain cases the bronchi show ulcerations and necrosis and plugs of débris obstruct the smaller air passages. The lungs may be filled with edema, and the trachea as well. A watery and at times serosanguineous fluid may be present, with, later, a purulent or fibrinopurulent exudate. Edema of the alveolar cells and interstitial tissues, with coagulation necrosis, hemorrhage, thrombosis and infarction of the blood vessels, may be present in varying proportions at different sites of the lungs. Damage is likely to be spotty rather than general. This may be caused to some extent by bronchial obstruction, due either to inflammation or to bronchial spasm, which limits the passage of contaminated air to certain parts of the lungs. Both petechial and confluent hemorrhages take place. Large or small areas of deeply congested lung tissue are seen at autopsy,

with a thin, sanguineous fluid dripping from the surface. If death takes place at a later stage of the development of pulmonary edema, chronic bronchitis, bronchiectasis and abscess of the lungs may be found.

As a result of swelling of the alveolar cells, the absorption of oxygen at atmospheric pressure proceeds at a slower rate than normally and unoxygenated blood passes into the aortic stream. The narrowing of the smaller bronchi results in incomplete ventilation of some of the alveoli, with accentuation of anoxia. Finally, the presence in the alveoli and the respiratory passage of serum and mucus further complicates ventilation of the alveoli.

In cases in which there is constriction of the bronchi, due to spasm and inflammatory swelling of the mucous membrane, an increased respiratory effort takes place, with a resultant increase in the negative pressure within the lung during inspiration. Any increase in negative intrapulmonary pressure tends to aggravate edema of the lungs by producing a suction action on the pulmonary epithelium. The increased ventilation engendered by anoxia is apt to be followed by a lowering of the carbon dioxide tension in the blood, the acid-base equilibrium shifting to the alkaline side. In severe asphyxia, however, acidosis takes place, the low pH being due to incompletely oxidized acid metabolites.

When pulmonary edema has been present for a considerable period of time, the loss of serum in the lungs results in concentration of the blood, and the diminished blood volume and increased viscosity promote stasis and capillary thrombosis. This circumstance is an additional factor that makes for tissue anoxia and ultimately throws an increased burden on the heart, owing to the increased resistance in the pulmonary circuit. Death may ultimately take place from right-sided heart failure, peripheral circulatory failure or bronchopneumonia.

The routine prescription of rest, warmth and inhalation of oxygen-enriched air is helpful to a certain percentage of patients. The inhalation of air with a high percentage of oxygen, such as 50 to 70 per cent, diminishes the severe anoxia in cases of outspoken pulmonary edema and this protects the patient from a cardiorespiratory failure that might otherwise ensue. Furthermore, the volume of ventilation is diminished under these circumstances by inhaling air with a high oxygen concentration and in this way the pathologically elevated negative intrapulmonary pressure is diminished and the suction effect of a high negative pressure on the lungs is prevented.

In many cases of pulmonary edema treated with rest, warmth and the inhalation of air with a high oxygen concentration, the passage of serum from the capillaries into the alveoli continues and drainage through the respiratory passageway is impeded, with the ultimate development of bronchopneumonia and death. The administration of positive pressure to combat edema of the lungs produced by gas poisoning was suggested by Barach, Martin and Eckman[15] in 1938 in a paper dealing with the therapeutic advantages of positive pressure in the treatment of clinical pulmonary edema. Mention was there made of a case of edema of the lungs described by Norton[16] in 1897 in which a rapid clearance of the edema took place with the use of the Fell–O'Dwyer forced-respiration apparatus. Although a theoretical discussion of the mechanism was not given in Norton's report, the clinical result was carefully described and was unmistakably the result of the introduction of a laryngeal tube and the application of forced respiration under positive pressure. No previous studies on the application of positive pressure in the treatment of irritant pulmonary edema due to gas poisoning have been reported.

The use of positive pressure for the treatment of clinical pulmonary edema was suggested by Plesch[17] and an apparatus for providing it was used by Poulton[18] in cases of paroxysmal dyspnea — so-called "cardiac asthma" — and of bronchial asthma. No benefit was obtained when there was generalized heart failure.

Barach[19] and his colleagues developed apparatus for the administration of positive pressure, originally for the treatment of bronchial obstruction in intractable asthma and obstructive lesions of the respiratory passageway. These comprised a mask with a closed-circuit apparatus, a hood that fitted over the patient's head and made closure at the neck, and a mask in which the patient breathed during expiration against resistance, provided by exhaling at first through a rubber tube placed in water to a depth of 3 to 6 cm., and later through a variably narrowed orifice attached to the mask. These methods of applying positive pressure were found to be effective in many severe cases of edema of the lungs occurring during the course of pneumonia and acute failure of the left ventricle.

In 1909, Emerson[20] showed that pulmonary edema produced by the intravenous injection of adrenalin into rabbits could be consistently removed by artificial respiration through a tracheotomy tube in which the lungs were gently distended and then allowed to collapse. In 1917, Auer and Gates[21] confirmed these results and showed that tracheal stenosis accentuated the edema caused by adrenalin. Congestion and edema of the lung as the result of tracheal stenosis were shown by Moore and Binger[22] to be due to obstruction during the inspiratory cycle. Kernan and Barach[23] confirmed these observations and showed that expiring against a pressure of 4 to 5 cm. of water created no significant changes in the lungs, whereas inspiring against a negative pressure of 4 to 6 cm. caused congestion and pulmonary edema in the lower part of both lungs, with areas of emphysema at the periphery. The negative intrapleural pressure became steadily elevated when

animals were made to inhale through a constricted orifice. This elevation was decreased by the inhalation of a helium-oxygen mixture or by the administration of positive pressure during inspiration. The significant factor in the production of pulmonary congestion and edema due to narrowing in the respiratory passage appeared to be the pathologically elevated negative intrapleural pressure, which resulted first in an increase in pulmonary blood flow and later in a direct cupping action on the pulmonary capillaries. In experiments on animals, Barach, Martin and Eckman[15] showed that edema of the lungs produced by intravenous injection of adrenalin could be prevented by inhalation of air under positive pressure, which raised the intrapleural pressure toward the atmospheric pressure during expiration. In this experiment it was demonstrated that no heightened negative pressure existed in the intrapleural space, and that the effectiveness of positive pressure was due to the direct opposing pressure on the capillary epithelium in the lungs of a physical force that tended to counteract the internal hydrostatic pressure in the pulmonary capillaries. Another influence was that the positive pressure retarded, to some extent, the inlet of blood into the right side of the heart.

It may be mentioned at this point that Meltzer[24] in 1878, said that the origin of pulmonary edema was due to a disproportion between the working power of the left ventricle and that of the right ventricle of such a character that, the resistance being the same, the left side of the heart was unable to expel in a given unit of time the same quantity of blood as was the right side.

The effect of respiration under positive pressure of 3 to 10 cm. of water in normal persons and in patients with congestive heart failure and asthma has been studied by me and my colleagues.[15, 19, 22] The venous pressure was consistently elevated. During the application of a pressure of 6 cm. the venous pressure was elevated 2 to 3 cm. The circulation time in normal young adults was slightly prolonged, but in patients with heart disease the slowing was as much as ten to fifteen seconds. Although prolongation of the circulation time did not occur in all cases, the change when it took place was more marked in cardiac patients than in normal persons, in whom the prolongation when breathing against a positive pressure of 6 cm. averaged three and a half seconds. In a normal adult the effect of breathing against a positive pressure of 6 cm. resulted in an increased amount of air in the lungs, — approximately 400 cc., — with a lowering of the midposition of the lungs and a lengthening of the vertical diameter of the chest. The only contraindication to the use of positive-pressure respiration noted by Barach, Martin and Eckman[15] was that of peripheral circulatory failure. Since in shock a deficient return of blood to the right side of the heart is already present, the high intrapulmonary pressure produced by inhalation of air or oxygen under positive pressure may further prevent the customary entrance of blood into the right auricle. The clearing of pulmonary edema in clinical cases of edema of the lungs was later confirmed by Boothby, Mayo and Lovelace[25] and others.[26]

In summary, the effects of positive-pressure respiration include an increased intrapulmonary pressure, which lowers the pathologically elevated negative pressure in the lung during respiratory obstruction (Fig. 1); an increase in systemic venous pressure amounting to 40 to 50 per cent of the applied pressure; a prolongation of the circulation time, which is notably more marked in patients with congestive heart failure than in normal subjects; an increased volume of air in the lungs, with a lowering of the midposition of the lungs and an increase in the vertical diameter of the chest; and a decrease in the transverse diameter of the heart, shown in roentgenograms of rabbits' hearts.

The favorable results of the administration of oxygen and helium-oxygen mixtures under positive pressure in the treatment of ordinary cases of edema of the lungs suggest that it would be valuable in the treatment of irritant gas poisoning.[15] In a personal communication, Carlisle[8] has reported that the administration of oxygen under an expiratory positive pressure of 1 to 6 cm. of water is the most effective method of treating and preventing pulmonary edema due to irritant gases. No patient exposed to lung irritants has been lost since this procedure was adopted. Over 300 cases of such exposure have been treated, and at least 25 manifested signs of edema.*

The technic of applying positive pressure may consist of the use of the hood designed for the treat-

*Since this paper was prepared, Carlisle has made the following statement (*J. A. M. A.* 123:947, 1943):

Without significant bronchiolar obstruction and before advanced pulmonary edema has appeared, inspiration of oxygen under atmospheric pressure with expiration against a calibrated resistance of 6 cm. of water pressure has handled successfully all cases we have encountered.

While in general our approach, as well as the actual management of most of our cases, has been that of prevention, we are convinced from our own experience that the use of the 1 to 100 epinephrine solution combined with the administration of oxygen under positive pressure of 1 to 6 cm. of water may be recommended for active treatment of the advanced stages of pulmonary edema caused by certain noxious gases. In our experience this has been a far more effective method of handling frank pulmonary edema than any of the procedures hitherto suggested. We find that on check of our records for the past year and a half, we have had 316 cases in which only this method of treatment has been employed.

Furthermore, Evans (*New York State J. Med.* 43:2303-2305, 1943) has commented on the use of positive pressure in treating the irritant pulmonary edema that developed in victims of the Cocoanut Grove Fire in Boston. He states that good results were obtained with the employment of oxygen under positive pressure and that the results in 4 cases were "rather spectacular."

The following notes on a case of irritant pulmonary edema were kindly transmitted to me by Dr. E. A. Rovenstine, of New York City, who treated a patient with the aid of positive pressure. The significance of this case is considerable since the application of an expiratory positive pressure of 5 cm. was followed by a swift clearing of edema, and seemed specifically responsible for recovery:

A middle-aged woman admitted in the early morning on February 19, 1943, had been exposed to fumes of a chemical (undetermined, but may have been dimethyl sulfate). Exposure was about 9:00 p.m. the evening before, with no symptoms for a couple of hours. Lacrimation and burning of the eyes and throat were noted. Later the patient became short of breath. On admission she was dyspneic and had severe pain, copious secretions and some cyanosis. The respiratory rate was 30 to 40, and the heart rate 120. Her condition rapidly became worse.

Oxygen was administered through the nasopharynx. An hour later there were obvious pulmonary edema, extreme cyanosis, marked venous engorgement and severe pain. Her condition was rapidly becoming alarming. An O. E. M. positive-pressure mask was adjusted at 5 cm. pressure; the result was dramatic, and within 15 to 20 minutes the edema had cleared. A phlebotomy (200 cc.) was completed after improvement was noted from oxygen therapy. The subsequent recovery was essentially uneventful.

ment of obstructive dyspnea, in which a positive pressure of 3 to 6 cm. is applied, during both inspiration and expiration. This method is the most comfortable and effective one for positive-pressure breathing. Dyspnea is relieved, since the pressure during inspiration results in a swift lowering of the intrapleural and intrapulmonary negative pressure and, during expiration, in a maintenance of a wider lumen of the bronchial tree (Barach and Swenson[27]).

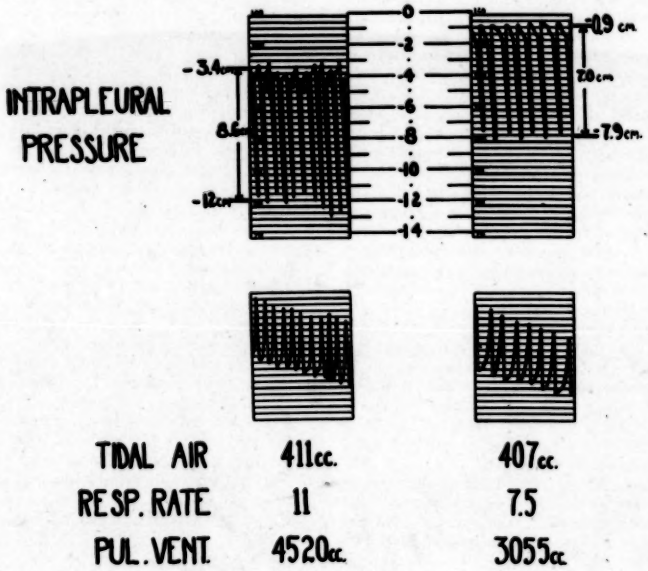

FIGURE 1. *Intrapleural Pressures and Tidal-Air Volumes in a Dog Breathing through a 5-Mm. Orifice.*

The tracings on the left were made with the air at atmospheric pressure; those on the right, with the air at 5.5 cm. water pressure.

The use of the mask with a closed-circuit rebreathing apparatus was employed in 1936 before the development of the hood. The apparatus is more cumbersome than the hood, since the removal of heat, carbon dioxide and moisture is necessary and depends on the continuous use of a motor-blower unit. A mask was then devised in which expiration takes place through a rubber tube inserted 3 to 6 cm. under water (Fig. 2).* The length to which the connecting tube is placed under water determines the extent of positive pressure within the mask and therefore the degree of pressure exerted on the respiratory passage and the inner surface of the lungs. Later, a simpler device was used in which expiration is conducted through one of a series of variably constricted orifices, the degree of constriction determining the degree of positive pressure exerted during expiration, so that a pressure of 1 to 4 cm. in expiration during quiet breathing is obtained (Barach and Molomut[28]). When the volume of ventilation is notably increased, a pressure of 4 cm. through the proper orifice results in a higher expiratory pressure. Recent measurements have shown that during expiration through the narrowest orifice an expiratory pressure of 10 to 12 cm. may result. The so-called "meter mask" with a pressure disk containing variably constricted orifices for expiration is the most convenient apparatus for administering positive pressure, but the degree of pressure actually received admittedly varies with the volume of ventilation, as described above. A rubber tube extended into a water bottle gives a more accurate expression of the actual positive pressure, but is more cumbersome. The metered positive-pressure mask may be calibrated by inserting a needle in the mask and connecting it by a rubber tube to a water bottle so that the degree of positive pressure can be accurately determined.

*Manufactured by the Oxygen Equipment Manufacturing Company, Incorporated, New York City.

In the treatment of a case of gas poisoning, both the degree and the duration of positive pressure are determined by a consideration of the factors discussed above. The administration of a positive pressure of 6 cm. may be sufficient to result in disappearance of edema in one to three hours. The pressure may be begun at 3, 4, 5 or 6 cm., depending on the co-operation of the patient. If pulmonary edema disappears during the application of a positive pressure of 3 to 6 cm. in a period of several hours, the pressure should be lowered to 2 cm. for one to two hours more. At the end of this time it should be lowered to 1 cm. for one or two hours and then removed. In other cases, if pulmonary edema has cleared, trials should be made of breathing without the mask for a period of five to thirty minutes, and if coughing and edema do not supervene, treatment should be discontinued. In the event that coughing and signs of pulmonary edema recur, the mask should be reapplied and positive pressure used for as long as necessary.

When pressure is applied during the expiratory cycle alone, there is less apt to be any noteworthy interference with the return of blood to the right side of the heart, since blood may enter the lungs during the inspiratory cycle, in which a negative intrapulmonary pressure naturally facilitates the inlet of blood into the right auricle. When pressure is applied within the hood, lower pressures should be used, since positive pressure is then exerted on the pulmonary capillaries in both inspiration and expiration. A pressure of 3 cm. of water has been found to be effective in terminating clinical pulmonary edema, although one of 4 to 5 cm. may be used in severe cases. Experience with the hood has been limited to cases of clinical pulmonary edema, only masks having been employed by Carlisle for the treatment of gas poisoning.

FIGURE 2. *Mask with Positive Pressure in Expiration.*

Although the administration of air containing 40 to 100 per cent of oxygen may be indicated in frank pulmonary edema in which severe arterial anoxia is present, the use of positive pressure with atmospheric air may be all that is required in the prevention of pulmonary edema after gas poisoning. Further studies are necessary to confirm this opinion. If gas poisoning has occurred in combat areas or in localities where oxygen in cylinders is not immediately available, the metered positive-pressure mask may be used by detaching the collecting bag and the rubber tube. Under these circumstances the patient inspires through the inspiratory valve that connects with the outside air; during expiration the inspiratory

valve closes and the expired air passes outward through a constricted orifice representing a pressure of 2 to 10 cm. of water. Since the permeability of the pulmonary capillaries as well as of the capillaries in the respiratory passage may be altered so as to produce oozing of both serum and mucus, inhalation against positive pressure tends to prevent the onset of the syndrome by neutralizing the internal hydrostatic pressure within the capillaries. Further experience is necessary to determine the range of effectiveness of this method. A three-hour period of breathing against positive pressure is recommended, followed by a gradual lowering of the pressure to that of the atmosphere for one to three hours longer, depending on an estimation of the severity of exposure.

If the metered mask is used with air, the inner surface of the mask should be equipped with an additional emergency inspiratory valve so that a plentiful inlet of air will take place without negative pressure's developing within the mask, even under conditions of severe dyspnea. If mixture of air and oxygen are to be provided, the metered mask, equipped as it is with an injector attached to the regulator, should be employed. With this apparatus oxygen and air are mixed at the regulator and a high flow of the oxygen-enriched air is passed into the collecting bag. The B.L.B. mask[39] can be used for the treatment of pulmonary edema if the flow of oxygen used is sufficient to keep the rebreathing bag from completely collapsing during inspiration. If the bag collapses, a negative pressure develops while air is being drawn through the sponge-rubber disks. Another way of using this apparatus without negative pressure's developing in the mask is to fit it so loosely to the face as to do away with the need for the disks.

Since the prolonged administration of 100 per cent oxygen is itself productive of pulmonary edema in animals, and since the specific therapeutic measure is the application of positive pressure, the employment of air containing 40 to 70 per cent of oxygen under positive pressure is recommended rather than that of 100 per cent oxygen. In the prevention of pulmonary edema, inhalation of air under positive pressure is likely to be adequate. In the absence of a mask, the patient should be instructed to exhale through partially closed lips or through a partially closed glottis, as in grunting respiration, thus naturally increasing the intrapulmonary pressure during expiration.

Another procedure of value is the inhalation of the nebulized spray of 1 per cent epinephrine or 1 per cent Neo-Synephrine at intervals of two to three hours. The former is especially valuable in cases of bronchial spasm, and the latter in patients in whom the congestion of the airway is the result of edema. Although the nebulization of these solutions may be accomplished to some extent by hand bulbs, a more effective method is the passage of 5000 cc. of oxygen from a high-pressure cylinder into a nebulizer containing 0.5 cc. of 1 per cent epinephrine solution or 0.5 to 1.0 cc. of 1 per cent Neo-Synephrine solution (Richards, Barach and Cromwell[39]). These drugs should be administered by inhalation, the end of the nebulizer being held within the mouth, at intervals of two to three hours. The enlargement of the diameter of the bronchial tree, either by diminishing bronchial spasm or by vasoconstriction of the mucous membrane, may be of definite help in decreasing the negative pressure necessary to inhale either air or the therapeutic atmospheric mixture administered.

Summary and Conclusions

The inhalation of oxygen and helium-oxygen mixtures under positive pressure has been shown to be of value in the treatment of cases of obstructive dyspnea and acute pulmonary edema commonly seen in the practice of medicine. The only contraindication to positive-pressure respiration described is the presence of shock.

The employment of positive-pressure respiration in cases of industrial gas poisoning indicates that edema of the lungs may be prevented and, when it has occurred, tends to respond to the administration of positive pressure in a far more successful way than under any hitherto suggested procedure.

A pressure of 3 to 6 cm. of water is usually effective in the treatment of pulmonary edema. If all signs of edema have cleared, a gradual reduction of pressure over a period of hours is recommended. Prevention of pulmonary edema after exposure to an irritant gas is advocated by inhalation of air or oxygen against positive pressure for two to three hours and then institution of trial periods of freedom from positive pressure to determine whether or not edema intervenes. Since pulmonary edema may take place as late as twelve hours after exposure, means for providing positive pressure should be at hand in any case in which known contact with a poisonous gas has occurred.

The inhalation of a spray containing 0.5 cc. of 1 per cent epinephrine is helpful in those cases in which bronchial spasm is present, and inhalation of 0.5 to 1.0 cc. of 1 per cent Neo-Synephrine is suggested to increase the lumen of the tracheobronchial tree by vasoconstriction.

In civilian disasters in which phosgene or other gases are liberated, the immediate administration of positive pressure is suggested. Although inhalation of oxygen-enriched air overcomes the arterial anoxia, prolongs life, and in some cases saves it, many cases exist in which continued outpouring of serum takes place, with impairment of bronchial drainage, secondary infection and bronchopneumonia. Although the sulfonamide drugs may be used to prevent infection, the primary pathologic condition is that of a hemorrhagic inflammatory edema, with infection only secondarily produced as

a result of bronchial obstruction. The use of rest, warmth, oxygen and the sulfonamide drugs is not considered on the basis of the evidence presented in this paper to be as valuable as is the employment of positive pressure. The latter procedure may prevent pulmonary edema, the consequences of bronchial obstruction, and bronchopneumonia.

There are in all probability many patients who are overcome to such an extent that death results almost immediately. The program of therapy outlined in this paper applies to those cases in which the possibility for therapeutic measures exists. Until more experience is forthcoming, the procedure of positive-pressure respiration must be regarded as offering a hope of combating irritant pulmonary edema and a legitimate although tentative program of therapy.

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NORMAL AIR ENCEPHALOGRAMS IN PATIENTS WITH CONVULSIVE SEIZURES AND TUMOR OF THE BRAIN*

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WHEN convulsive seizures develop during adult life, the clinician usually considers the possibility that they are a manifestation of some underlying structural lesion in the brain. He therefore studies the patient to exclude the known causes of seizures in adults. Visualization of the ventricles and the subarachnoid spaces by ventriculography or encephalography is one of the tests that are relied on to diagnose or exclude a neoplasm as the cause of the seizures. If the ventricles are found to be of average size and normally placed, the diagnosis of cerebral neoplasm is considered to have been excluded. The fallacy§ in such an assumption is emphasized by the three case histories given below. These patients had convulsive seizures and each had at least one normal pneumoencephalogram, yet each was eventually proved to have a brain tumor. The duration of seizures before the final diagnosis was established was four, four and a half, and six and three-quarters years, respectively. The first patient had a normal air encephalogram two and a half years after her first convulsion (seventeen months before discovery of the tumor). The second patient had a normal air encephalogram seven months after her first seizure (nearly four years before discovery of the tumor). The third case was the most instructive of all. The patient had two air encephalograms, the first of which, ten months after the first seizure, was interpreted as normal, while the second, ten months later, was considered to show doubtful cortical atrophy on the right, but to be otherwise normal.

Case Reports

Case 1. H. V., a 38-year-old, married woman, entered the Neurologic Service of the Boston City Hospital on December 1, 1938, because of two generalized convulsions, the first of which occurred 6 weeks before entry. So far as she knew, none of her family had ever had seizures. She herself had had rheumatic fever 15 years previously, and had been deaf in the right ear since an attack of measles in childhood.

Except for a deafness of the middle-ear type on the right there were no abnormal physical findings. The visual fields were normal. Routine blood and urine examinations were normal. The blood nonprotein nitrogen was 26 mg. per 100 cc., and the fasting blood sugar 80 mg. A blood Hinton reaction was negative. Lumbar puncture showed an initial pressure of 60 mm., 2 white cells per cubic millimeter, a total protein of 27 mg. per 100 cc., a gold-sol reaction of 0000000000 and a negative Wassermann reaction. X-ray films of the skull showed evidence of chronic mastoiditis on the right. An electroencephalogram showed no evidence of any focal abnormality.

The patient was discharged on 4½ gr. (0.3 gm.) of Dilantin and 1½ gr. (0.1 gm.) of phenobarbital daily and was seen at regular intervals as an office patient. She continued to have seizures of grand-mal type every 1 or 2 months on a daily dose of Dilantin ranging from 4½ to 7½ gr. (0.3 to 0.5 gm.) and 1½ gr. of phenobarbital, which was later replaced by 3 gr. (0.2 gm.) of Mebaral. A supravaginal hysterectomy was performed in January, 1941, because of dysmenorrhea. The removed organ was said to be normal. In the following June, the patient is said to have had a right-sided seizure with loss of consciousness. Because her family had also noted some personality changes she re-entered the hospital for study in that month.

On examination the patient seemed mentally dull and slow. There was some ataxia of the left leg on a heel-to-knee test, and the right (*sic*) plantar response was occasionally extensor. An air encephalogram was done on June 9, by the lumbar route. There was some subdural air on the left and a possible shift of the ventricular system to the left, which it was decided was an artefact due to rotation of the head. The spinal fluid had a normal protein content and colloidal gold reaction.

In the course of the next 1½ years, the patient continued to have monthly seizures despite treatment with Dilantin and Mebaral. She exhibited a marked personality and later intellectual deterioration, which led to institutionalization in February, 1942. In October, she developed a left-sided hemiparesis, headache and vomiting and was readmitted to the Boston City Hospital in November.

At that time the diagnosis of brain tumor was obvious. The patient was drowsy and apathetic and had bilateral papilledema and a left-sided hemiparesis, with a positive Babinski sign and a grasp reflex in the left hand. The cerebrospinal-fluid pressure was 305 mm., but the fluid was otherwise normal. An electroencephalogram showed a right frontal focus. On operation 3 days after entry a right-frontal astrocytoma was found that measured 6 cm. in diameter on the surface and extended 5 cm. into the brain substance.

Case 2. G. L., a 27-year-old, married woman, was admitted to the Neurologic Service of the Boston City Hospital on March 18, 1937, because of three convulsive seizures during the preceding month. Each seizure began with numbness and twitching of the left arm, and possibly the left leg, which was soon followed by loss of consciousness lasting 5 to 10 minutes. In one seizure the patient bit her lip. She seemed drowsy after each seizure and complained of numbness of the lips for an hour or two. There was no family history of epilepsy. The patient had had one convulsion in infancy. She was in the 6th month of her first pregnancy at the time of entry.

Physical examination was essentially normal. There was slight puffiness of both ankles, and the tendon reflexes were generally hyperactive. One examiner noted a sustained clonus of the left patella but this was not confirmed by others and there were no pathologic reflexes, weakness or sensory disturbances. The visual fields were normal. The blood pressure was 120/70. The urine was normal except for the slightest possible trace of albumin on one occasion. There was a mild normochromic anemia, with the hemoglobin 69 per cent (Sahli) and the red-cell count 3,540,000. The blood nonprotein nitrogen was 20 mg. per 100 cc. and a blood Hinton reaction was negative. Lumbar puncture showed an initial pressure of 150 mm., no white cells, a total protein of 13 mg. per 100 cc., a gold-sol reaction of 0000000000, clear color and a negative Wassermann reaction. X-ray films of the skull were normal.

The patient had one seizure while in the hospital. This began with twitching of the left leg, which was soon followed by loss of consciousness, after which the seizure became generalized. The entire seizure lasted 90 seconds. The patient was discharged on 1½ gr. of phenobarbital daily. She

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§Pennybacker, J., and Meadows, S. P. Normal ventriculograms in tumours of cerebral hemispheres. *Lancet* 1:186-190, 1938.

had four or five more seizures during pregnancy, of which at least some consisted only of weakness in the left arm and leg and shaking of the left leg for 2 minutes without loss of consciousness.

Seven months after the onset of symptoms, following a normal delivery, the patient entered another Boston hospital for observation. Extensive blood-chemistry studies yielded consistently normal results. Lumbar puncture was repeated and the findings again were normal (initial pressure 120 mm., total protein 34 mg. per 100 cc., and other results as before). X-ray examination of the skull was said to show thinning of the posterior clinoid processes, but an air encephalogram by the lumbar route showed the ventricles well outlined, with no abnormalities.

The patient continued to have six to ten seizures a year, at intervals ranging from a few days to five months, until March, 1939, when 4½ gr. (0.3 gm.) of Dilantin was added to the daily medication. With this she was seizure free for 2½ years. In September, 1941, she had another attack of numbness, followed by shaking of the body which she could not localize; there was no loss of consciousness. A careful neurologic examination at that time was negative except for slight horizontal nystagmus. An electroencephalogram in January, 1942, showed a focus of abnormal activity in the right motor area.

The patient tried to take larger doses of anticonvulsant drugs but could not because of dizziness and inco-ordination, especially on walking. She continued to have left-sided attacks without loss of consciousness, consisting in a feeling of weakness of the affected side, with the occasional addition of twitching of that arm or leg or both. By September she was having about one such seizure a week. Neurologic examination at that time revealed only weakness of the left leg, without abnormal reflexes or sensory disturbances.

Despite the lack of severe or frequent seizures the patient's general condition grew progressively worse, and by October she felt so weak that she stayed in bed most of the time. On November 16, she was operated on and a paramedian astrocytoma was removed that measured 14 by 8 cm. on its superior surface and ran down the entire depth of the falx to the corpus callosum.

Case 3. W. R., a 19-year-old, unmarried man, was admitted to the Neurologic Service of the Boston City Hospital in December, 1936, because of convulsive seizures beginning 9 months previously. The maternal grandmother had had epilepsy, and the patient had had three severe injuries at 1, 7 and 12 years, all to the left parietal region, at least one of which had fractured the skull. At first the seizures consisted of severe pain in the right arm that spread to the right leg, lasting less than a minute, followed by numbness, transient aphasia and generalized weakness. Later the seizures were accompanied by tonic movements of the right arm (chiefly extension) and shortly before entry the attacks began to be accompanied by loss of consciousness.

Physical examination on entry was entirely negative, as were routine blood and urine examinations, the blood Hinton reaction, x-ray films of the skull and an air encephalogram by the lumbar route.

The patient was discharged on 2¾ gr. (0.15 gm.) of phenobarbital daily, but his seizures grew more severe and frequent, and in April, 1937, he was started on 4½ gr. (0.3 gm.) of Dilantin daily. This was later increased to 7½ gr. (0.5 gm.) daily. The seizures improved somewhat with this treatment, but in September, 1937, he was readmitted to the hospital. This time there was some weakness of the right arm and deafness of the middle-ear type on the left. Routine laboratory examinations were again normal. Another air encephalogram showed normal filling of the lateral ventricles, which were normal in size and position. The films were said to show a possible diffuse cortical atrophy on the right (*sic*).

The patient then went to another Boston hospital, where a radical left mastoidectomy was done in November, 1937, without relief of symptoms. In February, 1938, a craniotomy was performed there and the left parietal lobe was exposed. The left motor area was found to be atrophic. According to the operative note, the pathology was so obvious that no attempt was made to stimulate the cortex. The patient was discharged on 3 to 4½ gr. (0.2 to 0.3 gm.) of phenobarbital daily and continued to have daily seizures.

The patient was readmitted to the Neurologic Service in August, 1938. For the first time a right lower facial weakness was noted. Routine studies were normal, but lumbar puncture was not performed.

For the next 4 years the patient spent much of his time either in the Boston City Hospital, the Monson State Hospital or the Boston State Hospital. He exhibited progressive personality deterioration and continued to have frequent seizures despite anticonvulsant therapy. The seizures were usually of the type described above, but generalized seizures of grand-mal type also occurred, and even on occasion seizures localized to the left arm. No changes were noted in the neurologic examination, and the right lower facial weakness persisted unchanged.

In November, 1942, the patient was admitted to the Boston Psychopathic Hospital because of aggressive behavior toward his family, urinary incontinence and failing memory. Physical examination revealed bilateral papilledema of 3 to 4 diopters and right lower facial weakness. Visual acuity was markedly reduced. On December 19, a craniotomy was performed immediately after a ventriculogram, and an extremely large fibrillary astrocytoma that had practically replaced the left temporal lobe was removed.

Summary and Conclusions

The records are presented of 3 patients with convulsive seizures who had normal air encephalograms, seven, twenty and thirty months, respectively, after their first convulsions but who were subsequently proved to have brain tumors. All three tumors were astrocytomas, one in the left temporal lobe, one in the right motor area and one in the right frontal lobe.

Although brain tumors are among the rarer causes of convulsive seizures, such tumors may cause convulsive seizures without producing any demonstrable distortion of the ventricular system. Cerebral tumors are not apt to produce any change in the ventricular system unless they are large enough to produce focal neurologic signs or increased intracranial pressure, as evidenced by choking of the disks or increased cerebrospinal-fluid pressure on lumbar puncture. If in the absence of these it is decided that an air study is advisable, a negative report should not be accepted as conclusive proof that no tumor is present.

MEDICAL PROGRESS

CARDIOGENIC SHOCK*

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BOSTON

IN VIEW of the fact that inadequate cardiac output appears to be the most important direct cause of the clinical picture of shock, it is somewhat singular that in the majority of cases peripheral rather than central circulatory defects are at fault. It is also somewhat singular that wider recognition has not been given to the possibility that shock may result from sudden diminution of cardiac output due to factors inherent in the heart itself. It is generally known that the shock syndrome may arise in a variety of diseases affecting the central circulatory apparatus, but many clinicians feel the necessity of assuming the presence of peripheral vascular collapse in such cases. Even in traumatic shock, the possible importance of heart failure as a sustaining factor has recently received attention,[1] and physiologists have long recognized the importance of cardiac mechanisms in maintaining blood pressure and blood flow.

Clinicians have been accustomed to thinking of all types of shock as having a similar pathogenesis—namely, an insufficient effective circulating blood volume. This point of view has been fostered by the concept that all cases of shock can be attributed to a disproportion between the circulating blood volume and the size of the vascular bed. Atchley[2] first applied this criterion to both surgical and medical shock, and it has been subscribed to by Blalock[3] and Moon.[4] This definition has the appeal of conciseness and reasonableness, but it leaves out of account the possibility that simple redistribution of blood, with depletion of the arterial side, can occur, and that shock may appear in the absence of any significant reduction of blood volume or increase in the total vascular bed.

That shock can occur in the presence of high venous pressure and adequate filling pressure of the heart is evidenced by the fact that the condition is often seen terminally in patients with chronic congestive heart failure due to hypertension or aortic valvular disease.[5] Since many clinicians depend on differentiating shock of peripheral origin from shock of central circulatory origin by means of the peripheral venous pressure, it remains to consider whether shock due solely to heart failure can occur in the absence of peripheral venous engorgement, and to inquire into the evidence for and against this possibility.

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It is first necessary to review briefly some fundamental facts that must be kept in mind if confusion is to be avoided. It must be readily apparent that the state of the peripheral veins is dependent largely on arterial inflow, and that the reduced arterial inflow to the superficial structures in shock results, other things being equal, in collapsed superficial veins. This applies in a somewhat lesser degree to the veins of the neck. Adequate filling of the heart, however, depends on the effective pressure in the auricles — that is, the height of auricular pressure above intrathoracic pressure — and not on the pressure in the superficial veins. Right auricular pressure (referred to as atmospheric pressure) in traumatic shock[6] has been measured and found to be low, but has apparently never been measured in cardiogenic shock. In some forms of the latter, however, the pressure in the femoral vein has been found to be significantly higher than that in the antecubital vein.[5] Furthermore, the peripheral manifestations of shock are dependent on a diminished output of the left ventricle, the filling pressure of which cannot be gauged by pressure in the right auricle, and even less by pressure in the peripheral veins.

Another important question is whether or not additional blood can be accommodated on the venous side of the circulation without unduly distending any vein or significantly raising the pressure within it. There can be little doubt that in the normal person a venous reservoir exists in the form of unused channels, and that even the channels in use can accommodate more blood without demonstrable effects on the pressure within the veins. The rapid intravenous infusion of large amounts of fluids can be accomplished in normal persons with only a slight and fleeting rise in venous pressure. Obviously, the amount of additional blood that the venous system can accommodate depends on how well filled the venous system is to begin with, and this is a function of the volume of circulating blood. It has been shown by Gibson and Evans[7] that the circulating blood volume is regularly increased in congestive heart failure, and that the increase begins with early loss of cardiac reserve and does not depend for its inception on marked congestive failure. It is apparent, therefore, that a cardiac event in a patient with a somewhat increased circulating blood volume may result in a combination of shock and congestive failure, whereas the same event occurring in a patient with a normal blood volume may result in a clinical picture of shock only.

Support for this reasoning is commonly found in patients with acute myocardial infarction. When this event occurs in a patient previously suffering from congestive failure or loss of cardiac reserve, the striking circulatory alterations are likely to be predominantly manifested by an increase in the signs of congestion, whereas in patients who previously were well the signs of shock are likely to prevail.[8]

Further support for and discussion of the importance of the circulating blood volume, as well as other peripheral mechanisms, in determining the venous pressure in heart failure are offered by Starr, Jeffers and Meade.[9] These investigators produced severe damage to the right ventricle of dogs, with resultant dilatation and failure of that chamber, without any significant increase in venous pressure. They were led to conclude that the results "give no support to the view that the peripheral venous congestion and the large increment of venous pressure so often associated with cardiac disease in man are caused directly and predominantly by failure of the right ventricle." In other words, heart failure seems to be less important in determining venous pressure than is blood volume or other unknown factors.

One further point in orientation needs to be considered. There are two clinical entities commonly producing the picture of shock that are due to central circulatory faults but not to failure of the heart as a pump. These are the rapid accumulation of fluid in the pericardial sac and massive pulmonary embolism. In both, striking engorgement of the neck veins is usually present and, since this may occur in previously normal patients with presumably normal blood volume, it has been taken to mean that sudden heart failure in previously well patients also results in engorgement of the peripheral veins. This line of reasoning contains an evident fallacy, for in pericardial effusion and in massive pulmonary embolism the pulmonary circuit is largely eliminated as a potential reservoir, and hence the entire amount of redistributed blood must be accommodated in the peripheral circuit instead of in both peripheral and pulmonary circuits, as in sudden failure of the left ventricle. That the pulmonary circuit is a reservoir of no mean magnitude is apparent from the fact that even patients with an increased total circulating blood volume may have no peripheral venous congestion despite a marked increase in pulmonary congestion due to failure of the left ventricle.

Since it is generally conceded that a variety of central circulatory faults may give rise to a combination of shock and congestive failure, this discussion will be mainly concerned with the forms of cardiogenic shock that may, at times, occur with normal or low peripheral venous pressure. If convincing evidence that the clinical picture of shock alone is due solely to cardiac factors can be brought forward, there seems to be no need to invoke peripheral mechanism to explain shock when it occurs in patients with obvious congestive heart failure.

Tachycardia

Wiggers[10] states that increasing the heart rate from 80 to 180 per minute results in a gradual diminution of output per beat with an increasing or steady output per minute, but that at rates above 180 the increasing number of beats per minute is unable to compensate for the diminishing output and, consequently, the total output falls. When the tachycardia is of ventricular origin, the critical rate is somewhat lower because of the abnormal excitation and less efficient contraction of the ventricles. These rates apply to normal hearts, and there is clinical evidence, as well as theoretical reasons, for believing that lower heart rates may significantly reduce cardiac output when there is underlying heart disease. Harrison[11] states that the collapse type of cardiac failure may occur with extreme tachycardia — usually over 170 per minute. Wolff[12] studied the effects of tachycardia in 125 patients and had the following to say about shock:

> Although a fall in blood pressure was commonly observed during paroxysmal rapid heart action, in only 15 cases did collapse occur. . . . Four patients had normal hearts (1 with hyperthyroidism), 5 had mitral stenosis, 1 had free aortic insufficiency, 2 had angina pectoris, 2 had asymptomatic coronary-artery disease and 1 had recent cardiac infarction. . . . Four patients had congestive failure. . . . The ventricular rate was 200 per minute or more in 7, or almost half the cases, and was less than 150 in only 2.
>
> Three factors appear to be significant in the genesis of vascular collapse: extremely rapid ventricular rates, embolism and aortic valvular disease. . . . When extremely rapid ventricular rates are attained, all other factors may be absent and the heart may be normal. . . . In the presence of aortic valvular disease vascular collapse may occur even though the ventricular rate is significantly under 150 per minute. . . . Occasionally, in elderly patients, vascular collapse may occur with only moderately rapid ventricular rates, even though other contributing factors are not evident.

Sturnick, Riseman and Sagall[13] studied 21 patients with various types of ectopic tachycardia and found shock in 15. Dyspnea was usually, but not invariably, present, whereas congestive failure occurred only twice. Pulmonary edema was associated with the tachycardia in 4 cases. Only 1 patient in whom shock occurred, a sixty-five-year-old man, was thought to have no underlying heart disease.

Marshak[14] reported a case of circulatory collapse associated with the onset of supraventricular tachycardia at a rate of 215 per minute in a young woman with an essentially normal heart. This occurred post partum, and associated blood loss or other factors may have played a part in the genesis of the vascular collapse.

A few cases of extremely rapid ventricular rates have been reported. These have been collected by Edeiken,[15] who adds a case of his own. This occurred in a patient who was convalescing from acute myocardial infarction that had occurred twenty-four days previously. The onset of supraventricular tachycardia at a rate of 310 per minute resulted in vascular collapse without signs of congestive failure. In discussing other reported cases of extreme tachy-

cardia, Edeiken points out that although collapse or congestive failure may occur it is often surprising how little an occasional patient is incapacitated by ventricular rates as high as 300 or more.

In summary, it appears that tachycardia may produce the clinical picture of shock, in many cases without signs of congestive failure, but that it does not invariably do so. In patients with no underlying heart disease and with no other contributing factors present, shock does not occur at heart rates below 180, and probably but rarely at rates below 200. When underlying heart disease is present, rates well below 150 may produce shock. Since shock itself is commonly accompanied by heart rates of 150 or more, it becomes of some importance, in occasional cases, to determine whether the tachycardia is ectopic and whether underlying heart disease is present.

In view of the correlation of the presence of shock with the onset and offset of tachycardia, and the correlation of observed critical rates with expected critical rates, there appears to be no need to invoke mechanisms other than the cardiac one to explain the presence of diminished cardiac output with resultant shock.

Myocardial Infarction

Infarction of the heart is, of course, the cardiac accident most frequently associated with shock. Often there is clear-cut evidence of both shock and peripheral congestive heart failure, but many cases give clinical evidence of shock alone. Since the clinical findings in cases of shock associated with myocardial infarction are sometimes identical with those in traumatic shock, many clinicians have become accustomed to thinking of both as having a common cause. It is not to be inferred that this concept is universal, for Harrison[11] and many others have long held that shock in myocardial infarction is due to so-called "hypokinetic forward failure." Inasmuch as the therapeutic approach to this grave manifestation of infarction is necessarily guided by a correct understanding of its mechanism, it seems desirable to evaluate the present knowledge concerning it.

At the outset it should be emphasized that, save for neurogenic shock, none of the currently popular theories of traumatic shock can reasonably be applied to shock in myocardial infarction. Certainly, sufficient loss of plasma into the infarct to produce shock cannot well be imagined, and it seems unlikely that liberation of a histaminelike substance sufficient in amount to paralyze the systemic capillaries is of importance. The search for a toxic substance liberated by traumatized or ischemic tissue is periodically revived and has recently been investigated by Green.[16] He was able to produce a shocklike picture in animals by the injection of an extract of skeletal muscle that proved on analysis to be barium adenosine triphosphate. Whether this substance has anything to do with traumatic shock is still extremely doubtful, but in relation to the muscle damage occurring in myocardial infarction, it is pertinent to point out that Green found the lethal dose of the crude muscle extract to be roughly equivalent, in terms of fresh muscle, to one fifth of the body weight. He also pointed out that the bulk of muscle that must be submitted to trauma or asphyxiation in order to produce severe shock in animals or man is very large. Unless cardiac muscle contains this toxic substance in a content many hundred times that of skeletal muscle, it is apparent that the concept of the liberation of such a substance to account for the shock in myocardial infarction must break down. Furthermore, such explanations leave unaccounted for the fact that the size of the infarct post mortem cannot always be satisfactorily correlated with the presence or degree of shock during life.

Since a decrease in circulating blood volume is a frequent, though not invariable, finding in traumatic shock, attention has naturally been directed toward this possibility in cases of shock associated with myocardial infarction. Fishberg, Hitzig and King[17] investigated the circulating blood volume in patients with acute myocardial infarction and concluded that the shock was peripheral in origin. Critical analysis of their results, however, shows that significant reduction in blood volume occurred in only 1 case and that actually the average blood volume remained essentially unchanged. In the first edition of his book Fishberg[18] held to the peripheral origin of shock in myocardial infarction, but in a later edition he reversed this opinion.[5] The absence of a significant reduction in circulating blood volume has been confirmed in patients[5] and repeatedly in experimental animals.[19-21]

A slight decrease in plasma volume and a slight hemoconcentration have been observed in patients with shock and myocardial infarction.[5, 22] Stead and Ebert[5] attributed this to loss of fluid through the pulmonary capillaries subsequent to pulmonary congestion. It is likely that, in some cases, excessive sweating or vomiting is an equally important factor, for concentration of the blood proteins indicates loss of water rather than loss of serum or plasma. That the degree of reduction in blood volume is insufficient alone to produce the picture of shock now appears to be demonstrated beyond reasonable doubt.

Measurements of cardiac output in relation to shock in myocardial infarction have been hampered by the fact that the gravity of the illness in human beings has precluded the use of complicated and tiring procedures, and by the fact that shock is not invariably, or even frequently, produced by the ligation of the coronary arteries in experimental animals[19, 20, 23, 24] (a point of some importance that is further discussed below).

Grishman and Master[25] measured cardiac output in 5 patients with myocardial infarction by a phys-

ical method involving the determination of the velocity of the pulse wave. None of these patients were in shock, yet their cardiac outputs were significantly diminished. It seems reasonable to suppose that the cardiac output would be even more drastically reduced in the presence of shock. Starr and Wood[26] also computed the cardiac output — by means of the ballistocardiograph — in patients with acute myocardial infarction. They, too, found a significant reduction in cardiac output but, strangely enough, severe cases — including those with shock — showed, on the average, less reduction than those with signs of a mild illness. In correlating blood-pressure changes with changes in cardiac output, they state: "This reduction [in blood pressure] did not always run parallel to the diminution of cardiac output, and so was not the result of change in the latter. It should be considered another adaptive mechanism." In view of the suspicion, recognized by Starr himself, that the form and magnitude of the ballistocardiographic waves may be determined by factors other than cardiac output alone, their conclusions cannot be accepted as established. Indeed, it has been shown that, in cases of shock, the ballistocardiogram may give figures for cardiac output that are as high as 75 per cent greater than those obtained by simultaneous determinations made by the direct Fick principle, whereas the agreement in more normal subjects is closer.[6]

Gross, Mendlowitz and Schauer[19, 20, 22] found that the significant hemodynamic changes occurring in experimental coronary occlusion were a decrease in cardiac output and an increase in circulation time. The blood pressure did not fall significantly, a finding noted by others studying experimental coronary occlusion.[24] Mendlowitz, Schauer and Gross[21] also studied the effects of ligation of the coronary arteries in denervated hearts. In such preparations the decrease in blood pressure was more striking than was that in animals with intact nervous pathways. The authors attributed this to the fact that some of the nervous pathways for compensatory vasoconstriction were interrupted. Since the carotid sinuses were not denervated, their conclusions must be accepted with reservations. Inasmuch as the heart itself was completely denervated, however, their results did indicate that reflexes from the heart were not directly responsible for the decline in cardiac output or blood pressure.

Stead and Ebert[5] studied 6 patients with acute myocardial infarction and shock. In 3 of these the circulation time was moderately to markedly prolonged, and all showed x-ray evidence of pulmonary congestion. Massie and Miller[27] found x-ray evidence of pulmonary congestion in 12 of 16 patients with acute myocardial infarction, although rales were heard in only 7 patients.

In summary, it appears that the shock syndrome in myocardial infarction cannot be attributed to a decrease in venous return, for, in addition to the considerable number of patients who show actual peripheral venous congestion combined with shock, there is evidence, in the form of prolonged circulation time and pulmonary congestion in many cases, that pulmonary venous and left auricular pressures are high. Since the manifestations of shock are dependent on the reduced output of the left ventricle, it is obvious that the left auricular pressure is of greater significance than is the pressure in the peripheral veins. The evidence indicates, therefore, that the venous return to the left ventricle is more than adequate and that the fall in cardiac output with resultant shock cannot be attributed to the mechanisms that are thought to be important in traumatic shock.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 30081

PRESENTATION OF CASE

A thirty-nine-year-old housewife entered the hospital because a left thoracotomy wound had failed to heal in the course of fifteen months.

The patient had enjoyed good health until seventeen months before admission, at which time she suffered an attack of pleurisy followed by pneumonia and empyema. She was admitted to a community hospital where, two months after the onset of her illness, a thoracotomy with resection of a portion of the left tenth rib was performed. One of eleven sputum samples examined was reported positive for tubercle bacilli and she was accordingly transferred to a sanatorium, where, during a stay of three months, numerous sputum and gastric examinations failed to reveal tubercle bacilli by smear or by guinea-pig inoculation. During her stay she lost 19 pounds in weight. On one occasion, when her wound was irrigated, she claimed to have expelled some of the irrigating fluid from her mouth. At home, the wound continued to drain intermittently and was associated with a sense of pressure on the left side and back, increasing on urination or defecation. The material discharged varied in color from red and yellow to water-clear; its consistence varied from thick to thin. In the intervals when drainage ceased she developed a cough, which was productive of reddish or yellow foul-tasting sputum. The temperature varied from normal to 104°F., averaging 99. Shaking chills occurred about every six weeks. She had profuse night and day sweats and, for three months prior to admission, dyspnea on exertion. She vomited frequently, especially when trying to work and had lost 50 pounds in the course of her illness. For the week prior to admission, the sense of pressure in the left side developed into a sharp continuous knifelike pain involving the side and back of the left chest and the left flank, radiating down the lateral aspect of the left leg to the ankle. Empirin Compound afforded some relief. She also had burning on urination, but no frequency or hematuria. The menses had been irregular throughout the illness.

Physical examination revealed a pale, weak and markedly emaciated patient in pain. Small tender nodes were palpable in the left axilla, left groin and both anterior cervical regions. There was diminished expansion of the left chest. A sinus-tract opening was present in the ninth left intercostal space in the posterior axillary line. From this point, a tender, visible and palpable mass extended downward over the left flank to about the level of the crest of the ilium. The heart sounds were regular and rapid with a crescendo, snapping first sound. The blood pressure was 110 systolic, 55 diastolic. The left leg was held in flexion at the thigh (45°) and knee (90°). Edema of the ankles and feet was present, being greater on the left. Pelvic examination revealed exquisite tenderness in the left vaginal vault, and a mass was palpable in this area on rectal examination. There were numerous external hemorrhoids.

Examination of the blood revealed a red-cell count of 3,500,000, with 60 per cent hemoglobin. The white-cell count was 24,000, with 88 per cent neutrophils. The urine showed adequate concentration, with a specific gravity of 1.020, a + test for albumin and 4 or 5 white blood cells per high-power field. The stools were normal. The serum nonprotein nitrogen, sodium and cholesterol were within normal limits.

X-ray examination showed irregular areas of increased density obscuring the lateral chest wall. A defect was seen in the first portion of the left tenth rib, and from this defect a soft-tissue swelling extended down into the left flank. The lumbar spine appeared normal. Lipiodol injected into the fistula revealed a communication with a large cavity, apparently reaching almost to the midline, displacing the stomach, and probably the colon, medially and extending downward to a point slightly below the crest of the ilium. The lipiodol moved freely within this cavity, and some of it apparently entered the small intestine. On a film after injection, opaque material was seen in the right upper quadrant. A barium enema revealed ptosis of the entire colon, which appeared normal except for evidence of extrinsic pressure on the descending portion. There was no evidence of communication with the abscess cavity. Thin barium injected into the fistulous opening in the chest wall entered a many-fingered cavity seen to communicate with the small bowel. Some minutes later barium was seen in the stomach, although no direct communication was observed. Later, after a barium meal, no barium was observed to pass from the stomach into the sinus tract, which appeared to be in close association with the upper lateral wall of the body of the stomach. The barium passed into the duodenum and jejunum, the latter appearing to be several centimeters below the level of the sinus tract. An intravenous pyelogram revealed incomplete outlining of the left renal pelvis, with moderate dilatation and blunting of the calyxes. There appeared to be a small pressure defect over the central portion, with incomplete filling of the middle calyxes. A gastroscopy revealed a superficial

*On leave of absence.

gastritis but no positive evidence of a fistulous opening into the stomach. A catheter passed into the chest sinus for a distance of 12 to 15 cm. did not enter the stomach.

The temperature ranged between 97 and 103°F.

The patient received several blood transfusions, one of which was followed by a mild reaction. On the tenth hospital day, the flank abscess was incised and drained. Thick, green, foul-smelling pus was encountered. The abscess cavity was observed to lead up under the diaphragm, toward the fundus of the stomach and splenic flexure and down posteriorly to the tip of the spleen and along the belly of the psoas muscle. Cultures of abscess pus and of material drained from the chest sinus revealed *Staphylococcus aureus*, *Staph. albus*, a nonhemolytic streptococcus, *Bacillus pyocyaneus*, fusiform bacilli and a few colonies of colon bacilli; no fungi grew on Sabouraud's medium. Of several guinea pigs inoculated with this material one was negative, the others dying too soon for a diagnosis to be made.

The wound continued to drain profusely. In spite of numerous transfusions, a stubborn anemia persisted, the red-cell count ranging between 3,000,000 and 3,500,000. The hematocrit varied between 30 and 40 per cent. The white-cell count averaged 17,000, with 71 per cent neutrophils. Several urine examinations revealed large numbers of pus cells. The prothrombin time was persistently prolonged, varying from 25 minutes (normal, 16 minutes) to 37 minutes (normal, 20 minutes). The blood total protein ranged between 4.8 and 6.6 gm. per 100 cc., with an albumin-globulin ratio of 1.0 on one occasion. A bromsulfalein test was negative. A Congo red test showed only 15 per cent dye absorption after one hour.

Because of the stubborn anemia and the evidences of nutritional deficiency the patient was given large doses of vitamins and liver extract parenterally, as well as considerable amounts of adrenocortical extract, in an effort to improve her condition. She was also given large doses of vitamin K (Hykinone).

On the thirty-first hospital day, the flank incision was again explored and the communication of the abscess cavity with the chest sinus was laid open. A necrotic mass presenting itself in the wound was biopsied and was reported as acute and chronic pyelonephritis and perinephritis. On the day following operation a catheterized urine specimen showed gross hematuria, but the urine later contained only 2 or 3 red cells per high-power field, as well as 15 to 20 white cells. Urine culture was positive for colon bacilli on this occasion, as well as for *B. pyocyaneus*, *Staph. albus*, *Clostridium welchii* and fusiform bacilli. An abdominal paracentesis yielded 1700 cc. of straw-colored fluid, which was negative on culture; it had a specific gravity of 1.010 and was negative for acid-fast bacilli and tumor cells.

On the thirty-eighth hospital day, the patient had to be placed on tube feeding because of persistent vomiting. She continued to vomit, however, and expired two days later.

Differential Diagnosis

Dr. Richard H. Sweet: The fact that the thoracotomy wound failed to heal is of interest, since such a wound usually heals unless there is some residual disease.

The attack of pleurisy followed by pneumonia and empyema is another curious thing in this history. So-called "primary pleurisy" is usually caused by the tubercle bacillus. I suppose theoretically tuberculosis exists in the lung and then spreads into the pleural cavity, but ordinarily, tuberculous pneumonia does not follow pleurisy or empyema. The pleurisy follows the pneumonia. So I believe there is something peculiar about the chest situation in this case, and I doubt whether the chest lesion was the primary one. It seems to me that it probably was secondary to something below the diaphragm.

". . . numerous sputum and gastric examinations failed to reveal tubercle bacilli by smear or by guinea-pig inoculation." I should like to interpolate that in my opinion the patient did not have tuberculosis because few positive cases are missed in a sanatorium. We have occasionally seen patients in whom supposed acid-fast organisms were found and who were sent to a sanatorium, where no evidence of tuberculosis could be found. Such patients eventually return, and the correct diagnosis of a nontuberculous lesion is made later.

"On one occasion, when the wound was irrigated, she claimed to have expelled some of the irrigating fluid from her mouth." What does that mean? If she had a fistula between the empyema cavity and a bronchus she would not speak of expelling the fluid; she would have coughed and brought it up. Therefore I suggest that the communication must have been below the diaphragm or through the diaphragm into a loop of bowel or into the stomach. Of course one cannot argue too much from the way the record is worded; but if the wording is correct, she did not have a bronchopleural fistula. That raises the question whether she might not have had a lung abscess. Of course, a lung abscess that had perforated, with a resultant empyema, might produce a bronchopleural fistula after drainage of the empyema. But there is no mention of the fact that the pus was foul smelling early in the course of the disease.

"Shaking chills occurred about every six weeks." I do not know of any disease with such periodicity. That does not mean much to me.

Night sweats may go with tuberculosis of the lung, but they may accompany any type of sepsis. She had a right to have the dyspnea on exertion. Furthermore, she appeared to have been sick enough to lose 50 pounds in weight, and I do not believe one has to assume that she had carcinoma.

This is probably not a primary kidney lesion because she had no hematuria or frequency. She had

enough sepsis to account for the tender lymph nodes. The tender mass and the pain make one think that she had an abscess in the flank, and as the case develops, the whole question centers on the abscess in that region. She has psoas spasm, which indicates that it was a deep abscess extending along the course of the psoas muscle. Pelvic examination confirmed that impression because it revealed "exquisite tenderness in the left vaginal vault." In other words this abscess had burrowed its way down through the flank and into the pelvis, which is not at all uncommon. The diagnosis, I think, will be greatly influenced by the x-ray films.

There is reasonably good evidence, both clinically and by x-ray, of perinephric abscess, or possibly subphrenic abscess. I am inclined to think it was the latter.

"On a film after injection, opaque material was seen in the right upper quadrant." It does not say whether that was in a hollow viscus or in the peritoneal cavity. If it was in the peritoneal cavity, we must be dealing with a subdiaphragmatic abscess.

"Later, after a barium meal, no barium was observed to pass from the stomach into the sinus tract, which appeared to be in close association with the upper lateral wall of the body of the stomach." That is exactly where it would be if it were a subdiaphragmatic abscess. It appears that we have evidence of a fistula communicating with the jejunum but not with the stomach or with the colon.

There is no mention of a tumor or of an ulcer on gastroscopic examination.

DR. LAURENCE L. ROBBINS: In the chest films there appears to be something in the region of the left costophrenic angle that I think could be all pleural. There is nothing definite within the lung. These films show that the sinus tract passes anteriorly and divides into many small branches. I assume that this is the material that went into the small bowel, and on one of the large films we can see that it has appeared in the stomach. The one thing that is impressive is that there is no evidence of a visible outline of the left kidney, and the psoas shadow is obliterated. The stomach, except for displacement, is not abnormal.

DR. SWEET: The sinus leads into the abdomen, however.

DR. ROBBINS: It goes a considerable distance farther forward than one would expect to find the kidney. It extends to a plane anterior to the spine.

DR. SWEET: Dr. Robbins is anticipating me. I was going to say that this could not have been a perinephric abscess.

It is rather interesting to speculate why adrenocortical extract was given. Because of the fistulous tract I wondered about diarrhea, but there is no mention of it. She had some disease that depleted her.

DR. FRANCIS D. MOORE: The patient did not have diarrhea.

DR. SWEET: This patient, with months of observation under medical care, had several attempts made to prove or disprove the diagnosis of tuberculosis. I believe it is reasonable to exclude such a diagnosis. As I have said, the sanatoriums do not miss that diagnosis very often, and one guinea-pig inoculation in this hospital, after the lapse of a proper length of time, showed no evidence of it. Therefore we must come down to a consideration of the etiology of a large subdiaphragmatic or perhaps perinephric abscess.

Perforation of a perinephric abscess into the abdominal cavity is a most unusual occurrence. I do not recall seeing it. Dr. Colby, who has seen many more perinephric abscesses than I have, tells me that he has seen only one that ruptured into the abdomen. We must always keep the two things entirely separate. Therefore, if my reasoning so far is correct, we are dealing with an abscess in the left upper quadrant of the abdomen, a subdiaphragmatic abscess that has done a number of things — namely, perforated through the diaphragm to cause empyema, extended into the pelvis and produced pyelonephritis. I have perhaps excluded the lung and pleural cavity as the source of all this mischief a little too rapidly, but there is no mention of anything that makes me think she had disease in the lung. The x-ray films do not show any residuum of disease in the lung, and the story suggests that she had something going through the diaphragm, and as we see later, she had a fistula. An empyema rarely perforates into the peritoneal cavity; on the other hand, a subdiaphragmatic abscess frequently perforates into the pleural cavity. Thus, the current is the other way. With these apologies, I shall exclude the chest as the source of the disease.

If there was a subphrenic abscess, either intraperitoneal or abdominal, where did it come from? A subphrenic abscess always arises from some septic focus within the abdomen. The commonest cause is a perforated viscus, such as a ruptured gall bladder, appendix or diverticulum, or through a malignant tumor in a hollow viscus. Occasionally a liver abscess perforates and causes a subphrenic accumulation of pus, but that is unusual. Then there is the occasional case in which a picture like this can be explained entirely by acute pancreatitis. Some patients with necrosis of the pancreas develop large accumulations of pus, usually in the left part of the upper abdomen, which ulcerate into the viscera, perforate the diaphragm or gravitate down along the psoas muscle or even into the pelvis. In such cases, we sometimes drain the pancreatitis through the inguinal region because the abscess has presented as a bubo in the groin, having gone all the way down by the retroperitoneal route.

There is one other condition that I have not mentioned because it did not seem to fit in very well. Could the trouble have started from an infection in the spine — an osteomyelitis? When I originally

thought of tuberculosis I wondered if it might have been a tuberculous lesion starting in the spine. The x-ray films do not suggest a spinal lesion, and the patient did not behave like one with osteomyelitis of the spine.

I should conclude my discussion by deciding whether this subdiaphragmatic abscess arose from a ruptured viscus or from an acute pancreatitis, but I cannot say which it was.

DR. CASTLEMAN: The field is still wide open.

DR. FLETCHER H. COLBY: The possibility of perinephric abscess is naturally good. My experience with a perinephric abscess that involves the peritoneal cavity is rare. In the only case that I can remember, the patient died very quickly. Whether it can involve the intraperitoneal contents without causing peritonitis, such as this individual had, I do not know.

DR. MOORE: When the patient came in on the surgical service she presented the enigma that Dr. Sweet has described: she had supradiaphragmatic and subdiaphragmatic sepsis, and the problems were how it got from one place to the other, and what was the origin. Our reasoning was guided by one fact that is not stressed in the abstract of the history. The original thoracotomy wound was at the level of the tenth rib in the midaxilla; this was too low for the drainage of an empyema, and was so low that one could with great ease penetrate through the diaphragm and perforate a subdiaphragmatic viscus. We thought that this accident had occurred, possibly with perforation of the splenic flexure, and that this gastrointestinal sepsis had swamped the whole region, including the kidney. Later on, as we got the x-ray films, it seemed that the viscus entered was not the splenic flexure but either the stomach or the small bowel. We continued working on that assumption—accidental perforation through the low thoracotomy site, which had allowed sepsis to be introduced into the abdomen from the gastrointestinal tract.

The patient was given adrenocortical extract because, along with the chronic pyogenic infection, she had evidence of adrenal insufficiency. The blood sodium was 120 milliequiv. per liter, and the 17-ketosteroids were low. We gave the extract in an effort to restore this endocrine imbalance.

FIGURE 1. *Actinomycotic Clumps in an Abscess of the Liver.*

CLINICAL DIAGNOSES

Subdiaphragmatic abscess, probably originating from perforation of intestine.
Pyelonephritis.

DR. SWEET'S DIAGNOSIS

Subdiaphragmatic abscess, originating from perforated viscus or acute pancreatitis.

ANATOMICAL DIAGNOSES

Actinomycosis of left retroperitoneal and retropleural spaces, left kidney and liver.
Perforation of splenic flexure of colon.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy on this patient showed what was to be expected—a large abscess in the left retropleural and retroperitoneal regions

extending from about the level of the fourth rib through the diaphragm down to the level of the head of the femur. It did communicate with the splenic flexure, and not with the small bowel. There was a definite fistulous tract between the abscess and the splenic flexure. The kidney on that side was practically destroyed by this abscess, and we were unable to find the left adrenal gland. We also noticed that the liver was full of abscesses of varying sizes, which contained yellowish-green material. We made a diagnosis of abscess (type undetermined), with abscesses of the liver, and thought that the patient had a terminal septicemia.

Microscopic examination of the wall of the abscess, as well as of the abscesses within the liver, showed large numbers of actinomyces. Hence, there was definite actinomycotic infection of the kidney, retroperitoneal space and the lower part of the left pleural cavity. The left lower lobe was completely collapsed, and we were unable to find any evidence of infection within the lung itself. Until Dr. Moore just said what he did about the rib resection, I was at a loss to explain how the actinomycotic infection arose. If it had arisen from the lung, as it often does, it would seem a little far fetched to believe that the infection within the lung disappeared and that the infection below the diaphragm continued. Also, a primary actinomycotic infection of the kidney is extremely rare; I think that it has been reported but it is ordinarily a secondary infection. I now believe that the perforation of the splenic flexure at the time of the rib resection released the organisms, which we know are often present in the normal colon. After the infection was well established, the portal vein was invaded by the organisms and a diffuse hepatic infection resulted.

DR. MOORE: Have you any explanation why the biopsy showed no actinomyces?

DR. CASTLEMAN: We reviewed this slide after the autopsy and still could find no evidence of actinomycotic infection.

DR. MOORE: I might also mention that Dr. Cora Owen, of the Surgical Bacteriological Laboratory, who is interested in the study of actinomycoses, was unable to culture them. There was a large quantity of material to work with, and it was planted on all kinds of mediums at varying oxygen tensions, but no organism grew out.

DR. CASTLEMAN: The liver abscesses were full of actinomycotic clumps (Fig. 1). It is the best case that we have seen since the days of Dr. J. Homer Wright.

CASE 30082

PRESENTATION OF CASE

A sixty-five-year-old man, a retired bank clerk, was admitted to the hospital with anorexia and epigastric pain.

About three months before admission the patient began to experience anorexia, associated with gnawing pain in the epigastrium and region of the umbilicus. The pain was worse early in the morning and from a half to two hours after meals, but was not relieved by food. It was associated with deep pain in the back, at about the level of the seventh to the ninth dorsal vertebra, and with increasing weakness and malaise. For several weeks prior to admission he had complained of frequent attacks of nausea after meals, aggravated by the ingestion of greasy foods. He also stated that his bowel movements, which had occurred regularly twice daily, altered to once a day. Twelve days before entrance into the hospital his bowel movements ceased entirely for a period of six days, during which time only flatus was passed, but a dose of castor oil brought relief. Two days before admission, after taking a drink of whisky, he had an episode of bilious vomiting. Over a period of nine months the patient had lost 40 pounds of weight, half of this in the two or three months prior to admission. He had had an early morning cough associated with a small amount of expectoration for as long as he could remember, but he first noted wheezing about six months before entry. The wheezing was most noticeable when he was lying down, and diminished when he sat up. In the two months before admission, he had also noticed that he could walk only short distances without becoming short of breath, and in addition, his ankles were somewhat swollen. No orthopnea was present.

At the age of ten, the patient had rheumatic fever and was confined to bed for three weeks. At about the age of twenty-five, he had a chancre of the penis associated with a positive Wassermann test, for which he was treated over a period of two years. At about the same time he had gonorrhea. Twenty years before admission he had an attack of pain in the right upper quadrant, associated with nausea and vomiting, and following this a cholecystectomy and appendectomy were performed. Five years before admission he had an attack of abdominal pain that was diagnosed as being due to intestinal obstruction. He was admitted to a hospital but was treated nonsurgically. The patient was a moderate smoker, but drank heavily, consuming about a pint of whisky daily until he ceased working several years before admission. Since that time he usually drank seven or eight glasses of beer daily. During the year prior to admission he developed pain in the shoulders and hips, which was aggravated by cold weather and caused some difficulty in walking. His mother had died of cancer of the liver.

Physical examination revealed a weak, poorly nourished man. The skin was rough to touch, and there was exfoliation over the shins. Circumscribed areas of pigmentation and exfoliation were present in the axillary and inguinal regions. Numerous telangiectases were present on the face. On the

buccal mucosa were numerous soft, blue, vascular nodules, some of which were lobulated. The scleras appeared icteric. The lungs revealed diffuse inspiratory bronchial rhonchi, and an area of dullness to percussion was present about a handbreadth below the right axilla, extending posteriorly and unassociated with changes in breath sounds. In the epigastrium a nodular mass could be felt extending seven fingerbreadths below the xiphoid process and to the left midclavicular line; the edge was blunted and tender. In the right midclavicular line the liver edge was palpable two and a half fingerbreadths below the costal margin. There was some tenderness, and a suggestion of a mass, in the left upper quadrant. The extremities revealed a fine muscular tremor, tortuous brachial arteries, cyanotic and brittle nails, and redness and mottling of the palms. The knee jerks were active, and the Babinski sign was positive bilaterally.

The blood pressure was 150 systolic, 110 diastolic. The temperature was 98°F., the pulse 88, and the respirations 20.

Examination of the blood showed a red-cell count of 3,920,000, with a hemoglobin of 15 gm. The white-cell count was 8000, with 78 per cent neutrophils. The urine was negative. The stools were loose, brown and guaiac negative. The van den Bergh was 1.6 mg. direct and 2.5 mg. indirect. The blood phosphatase was 10.5 Bodansky units per 100 cc. The blood nonprotein nitrogen, the carbon dioxide combining power and the chloride were within normal limits. The blood protein was 6.8 gm. per 100 cc., with an albumin-globulin ratio of 0.8. The cholesterol was 225 mg. per 100 cc. A cephalin flocculation test was ++ after twenty-four and forty-eight hours. A blood Hinton test was negative.

A gastrointestinal series showed displacement of the stomach to the left and anteriorly by a mass in the region of the liver, and a pressure defect was present on the lesser curvature. A barium enema revealed several diverticulums in the proximal portion of the sigmoid, but was not otherwise unusual. A roentgenogram of the chest showed an area of increased density in the left lower chest, blunting of the left costophrenic angle and a prominent left hilus.

The patient was given a high vitamin diet and intravenous fluids but failed to respond; he gradually became stuporous and comatose and expired quietly on the twentieth hospital day.

Differential Diagnosis

Dr. Friedrich W. Klemperer: This patient's chief complaint points toward involvement of the digestive system, and physical as well as x-ray examination demonstrated a mass that in all probability was the left lobe of the liver. There are a number of possibilities to explain the enlargement of the liver in this patient. He had had syphilis twenty-five years before admission and he could have had a syphilitic cirrhosis. We know, however, that he had immediate and apparently adequate treatment and his Hinton test was negative. Neither of these rules out late syphilis but taken together, as well as the fact that involvement of the liver in late syphilis is quite rare, they make this diagnosis highly improbable.

The patient was also an alcoholic, and portal cirrhosis of the liver is therefore a good possibility. Several statements in the record, however, are against cirrhosis as the chief source of his trouble. These are the extremely rapid progression of the symptoms, the emaciation and presumably the increase in the size of the tumor, the absence of ascites or evidence of collateral circulation and the absence of splenomegaly. All these facts, however, could be easily explained if the patient had developed a hepatoma on the basis of an early cirrhosis. This must be weighed against the probability of metastatic malignancy to the liver.

What is the evidence we have for a primary lesion elsewhere? The patient had had an attack of so-called "intestinal obstruction" five years before admission. The lack of progression and medical cure definitely rule out the presence of cancer of the bowel at that time. We know that he had diverticulosis at the time of admission, and his previous attack of abdominal pain can logically be explained as having been due to diverticulitis. The recent change in bowel habits seems unlike that usually seen in obstruction due to malignancy and can easily be explained as secondary to the liver disease. The stools were guaiac negative. I see no reason why we should doubt the x-ray evidence that there was no lesion in the large bowel. Similarly we have no evidence that leads us to place the lesion higher in the intestinal tract. Primary carcinoma of the pancreas must always be thought of because it so easily escapes clinical detection. This is an appealing diagnosis because it would explain the character and distribution of the patient's pain near the umbilicus and in the back. Such a lesion would have to have been located in or near the tail of the pancreas, because carcinoma of the head would have led to progressive and severe jaundice. Although primary carcinoma of the pancreas is a distinct possibility, I am going to discard it in favor of a primary lesion in the lungs.

It should be remembered that nine months before admission — that is, six months before the onset of abdominal symptoms — he began to lose weight. Definite respiratory symptoms also preceded the abdominal symptoms by three months. The patient complained of wheezing respirations and dyspnea. These symptoms, particularly in the absence of orthopnea, are highly characteristic of lung tumor. They are most frequently seen in bronchiogenic carcinoma but can also occur in metastatic malignancy. For two reasons I am inclined to believe that the pulmonary lesion was primary rather than

metastatic from a primary lesion in the liver or pancreas. The first is the fact that the pulmonary symptoms preceded the abdominal ones by several months, and the second, that Dr. Robbins tells me that the x-ray changes in the chest are unlike those seen in metastatic malignancy. The age of the patient and the clinical course seem consistent with the diagnosis of bronchiogenic carcinoma with metastases to the liver. I see no evidence in the record to make one consider seriously the possibility of lymphoma or even sarcoma.

There are several points in the record that require comment. The patient had skin lesions. I interpret these as having been due to nicotinic acid deficiency. The telangiectases do not seem to bear any relation to the patient's illness. Their description does not indicate that they were the spider angiomas sometimes seen in cirrhosis of the liver. The patient had joint pain. The multiplicity and symmetry of involvement are against metastatic disease. There are not enough data to differentiate degenerative joint disease and rheumatoid arthritis. The latter seems somewhat more likely in view of the joint disease that the patient had during childhood, then diagnosed as rheumatic fever. The laboratory data indicate some parenchymal involvement of the liver. This may mean that the patient had a cirrhosis of the liver in addition to metastatic disease, but it is known that extensive malignancy can produce these changes. The immediate cause of death was probably general malnutrition but possibly liver failure.

Clinical Diagnosis

Metastatic carcinoma of liver (?source).

Dr. Klemperer's Diagnosis

Bronchiogenic carcinoma, with metastases to liver.

Anatomical Diagnosis

Oat-cell carcinoma of lung, with metastases to regional lymph nodes, liver, pericardium, right adrenal gland and rib.

Pathological Discussion

Dr. Benjamin Castleman: The post-mortem examination disclosed a primary tumor in the lower or lingula branch of the left upper-lobe bronchus, with almost complete obstruction. The tumor involved about 4 cm. of the bronchus and had extended into the surrounding parenchyma. The carinal lymph nodes were involved and were matted together to form a 6-cm. mass. The lung distal to the tumor showed secondary bronchiectasis. The liver weighed 3000 gm., and about three fourths of it was replaced by metastatic cancer. Other metastases were present in the parietal pericardium, the right adrenal gland and one of the ribs. Microscopically the carcinoma is of the oat-cell type. This is the type that is usually located near the hilus and grows very rapidly.

We found no evidence of syphilis.

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A MARCH OF MERCY

As Red Cross Month comes around, the Nation is reminded once more of the American Red Cross and its stupendous task of relieving human suffering. The organization is national only in name, for its fighting fronts have been extended to every corner of the globe.

The immediate need is for blood donors and nurses. During 1944 the Red Cross must supply some 5,000,000 blood donations for military and civilian needs, and each month 2500 nurses must be received for the Army and Navy. In addition the large corps of field directors, hospital workers and other trained personnel must be kept at fighting strength, and where necessary increased. An important part of the war work is the preservation of morale in the armed forces by maintaining contacts between soldiers and sailors and their families, especially when domestic troubles arise. It goes without saying that, as ever, the American Red Cross must be ready to cope with disasters and epidemics at home, as well as with the endless needs of a nation at war.

All the activities of this vast organization are financed by voluntary gifts and contributions. During March, designated by President Roosevelt as Red Cross Month — in both senses a March of Mercy — the American Red Cross must raise a war fund of unprecedented size to meet unprecedented needs. More than ever, a generous answer to its appeal will be a gesture of patriotism and a sign of love for mankind.

PENICILLIN IN WOUNDS

Although only a small number of physicians in this country have had an opportunity to use penicillin, it is now fairly well established that this agent is highly effective in the treatment of many types of bacterial infection. It has already proved to be a lifesaving measure, surpassing the sulfonamide drugs in effectiveness under certain conditions. This has been particularly true in certain cases of staphylococcal septicemia and of meningitis. It is also highly effective in the treatment of infections with strains of gonococcus and pneumococcus that are resistant to sulfonamide therapy, and it may eventually prove to be the most effective agent in the treatment of syphilis and perhaps of other infectious diseases. The results of studies of the use of penicillin in surgical conditions in the past indicate that large doses are needed in the successful treatment of well-established wound infections, frequent doses of the drug being given parenterally and locally for long periods. In view of the limited supply now available, only a small percentage of established wound infections can receive the benefits of treatment with this agent.

The question naturally arises whether the early use of penicillin locally in fresh wounds wards off serious infections. Should it be possible thus to prevent infection in fresh wounds of soft tissue and

in compound fractures, obviously a large number of patients would be spared prolonged and severe illness and many limbs and even lives would thus be saved. Furthermore, this might readily be accomplished with a relatively small amount of penicillin and could, therefore, be made soon available for use in large numbers of battle wounds in the present conflict.

To investigate this aspect of the management of wounds, two eminent British investigators, Professor H. W. Florey, who has been intimately associated with the developments in penicillin therapy, and Brigadier Hugh Cairns, a leading surgeon, set out to make an intensive but brief study of the treatment of wound sepsis in North Africa. They had the collaboration of many medical officers and investigators. A detailed preliminary report of their findings was made to the British War Office and to Medical Research Council, and an abstract of this report has been published.[1] An additional study in Britain of the value of penicillin in infected burns and surface wounds is reported in the same issue of the *Lancet* by Flight Lieutenant D. C. Bodenham.[2]

In the investigations in the Mediterranean area local applications were made in four forms. The first was a solution of the calcium salt in distilled water or saline (250 to 500 units per cubic centimeter), and the second, a cream with lanette wax (250 units per gram). The latter holds penicillin in contact with tissues longer than is possible with a water solution and is itself soluble in water. The third form was crude, dried calcium penicillin applied directly to the infected surface, the penicillin dissolving in the fluid present. This method was thought to be unnecessarily wasteful because the powder is difficult to spread thinly over a large wound; furthermore, the powder, as such, is irritating when used locally. Finally, the powder, diluted with a sulfonamide, was insufflated on the infected area with a blower — sulfanilamide was used by Florey and Cairns, and sulfathiazole by Bodenham. The mixture contained 500 to 5000 units of penicillin per gram. In many cases it was necessary to supplement local treatment with parenteral therapy in large amounts.

A small number of chronic septic wounds of three to four months' standing were treated at Algiers. The results in these cases were not encouraging, and it was concluded that treatment of long-standing septic compound fractures would require large amounts of penicillin, which might be more profitably used in more recent wounds.

Early closure of soft-tissue wounds was carried out in 171 cases by ten surgeons at five general hospitals at Tripoli and Sousse. Most of these wounds were three to twelve days old when closed; they were usually infected, and some were actually purulent. As experience and confidence grew, it was found possible to close almost all wounds except those in which the missile had produced gross destruction of skin. The medical officers who carried out the treatment were most enthusiastic about the results of closure of recent fresh wounds, and one of them remarked that with penicillin the obstacle of infection had been practically overcome.

In the treatment of recent compound fractures the aim was to prevent chronic infection and to convert them as soon as possible into closed fractures by suturing the wound. The cases available had been temporarily immobilized in the forward area and were five to fourteen days old on arrival at the base hospital. In this group, intramuscular injections or injections by continuous drip of penicillin were used, up to a total of 500,000 units, in addition to the local therapy. The wounds were completely sutured, except for a few in which this was mechanically impossible. In summing up the results obtained in recent fractures it was thought that too much had been attempted in the way of wound closure. Thus, in a comminuted fracture, it seemed better to leave potential drainage to the exterior for the first week or ten days. It was also thought that the dosage in the compound fractures of the tibia and femur was too small — in other words, that a total of 700,000 to 1,000,000 units should be given over a period of seven to ten days, although this might prove unnecessary in patients who had received penicillin in the forward area.

Only a small number of cases of gas gangrene were treated. Although there was some evidence for a favorable effect, the final results were not encouraging: toxemia was not counteracted, and it was thought that fulminating cases could not be saved by penicillin alone. On the other hand, it was

stated that penicillin might be expected to play an important role in prevention.

The study of the use of penicillin in head wounds was chiefly limited to cases of penetrating brain injury of three to twelve days' duration. Almost all of them were infected with gram-positive pyogenic organisms, and about half were frankly suppurating. These wounds were excised, cleaned and closed, and injections of a solution of calcium penicillin were given every twelve hours for three days through a stab wound into the brain cavity. The average total dosage was 15,000 units. The penicillin-sulfanilamide powder was applied to the wounds during dressings and occasionally during operations, and a small number of patients with compound fractures in other parts of the body also received intramuscular doses of penicillin. The results in this group were encouraging. Gram-positive cocci usually disappeared from the wounds within forty-eight hours. The observers state that penicillin deserves an extensive trial in brain wounds for which definitive treatment cannot be given before seventy-two hours. For earlier cases they believe that the sulfonamides are adequately effective. Nonpenetrating wounds were successfully closed and treated with penicillin solution through tubes for three to five days, a total dose of only 3000 units being used. In scalp wounds not associated with fractures, healing by first intention was secured with a single application of 1 to 3 gm. of penicillin-sulfanilamide powder after excision.

Penicillin applications were also tried on a few burns that had remained persistently infected by hemolytic streptococci in spite of sulfathiazole by mouth and sulfadiazine locally. The response of these burns to extremely small doses of penicillin-sulfanilamide powder was uniformly rapid, and free grafts took satisfactorily in spite of the presence of pus containing gram-negative organisms. About 20,000 units was adequate in such cases.

No attempts were made by the British investigators to compare the results of penicillin therapy with those of other forms of treatment. Obviously this would have required extensive and carefully controlled studies and would have been futile unless it had been found that the penicillin itself was effective in the various conditions in which it was used. They therefore confined themselves to ascertaining the range of usefulness of penicillin in the treatment of wounds, and the best methods of applying this form of therapy. The present results merely suggest that penicillin treatment is feasible and useful under certain field conditions. No claims are made that it is better than any other form of therapy. How useful it is and how it will compare with the results obtained with sulfonamides and other forms of therapy remain for further study.

The divergent results reported from the use of sulfonamides in the treatment of wounds illustrate well how difficult such a problem can be. Early reports of sulfonamide therapy were most enthusiastic, whereas in later ones the optimism was considerably tempered. This is illustrated in Meleney's recent report of the Subcommittee on Surgical Infections of the National Research Council.[3] The members of this committee concluded from their extensive studies that sulfonamides minimize the general spread of infection in wounds and cut down the incidence of septicemia and death. They had no evidence, however, that the incidence of local infections was lessened by the sulfonamides as they have been employed. They state that, if the incidence of local infection in war wounds and burns is to be decreased, some other form of sulfonamide or some other bacteriostatic agent must be found that is effective against the contaminating organisms in the presence of damaged tissue. Penicillin is such an agent, and the studies of Florey and Cairns indicate that it may be useful by itself or as a supplement to the sulfonamides.

References

1. Florey, H. W., and Cairns, H. Penicillin in war wounds: report from Mediterranean. *Lancet* 2:742-754, 1943.
2. Bodenham, D. C. Infected burns and surface wounds: value of penicillin. *Lancet* 2:725-728, 1943.
3. Meleney, F. L. Study of prevention of infection in contaminated accidental wounds, compound fractures and burns. *Ann. Surg.* 118:171-186, 1943.

MEDICAL EPONYM

Stevens–Johnson Syndrome

"A New Eruptive Fever Associated with Stomatitis and Ophthalmia" was described by Albert M. Stevens (b. 1884) and Frank C. Johnson (1894–1934) of Columbia University and Bellevue Hospital in the *American Journal of Diseases of Children* (**24**: 526-533, 1922). A portion of the article follows:

> During a period of three months we had the opportunity of observing two cases of an extraordinary, generalized

eruption with continued fever, inflamed buccal mucosa and severe purulent conjunctivitis. . . .

. . . . No diagnosis could be made to correspond with the symptoms and course of the eruption in these two cases and no description was found of a skin condition in any degree comparable.

. . . . Here is a syndrome of dramatic onset, with fever, conjunctivitis and cutaneous eruption. The child is prostrated, the mouth and tongue are inflamed and raw, the eyelids are swollen and pus streams from the eyes. There is a course of three or more weeks of high fever, with leukopenia. The eruption, unlike any hitherto described, comes out progressively, for two weeks or more, matures and resolves in horny crusts, in the order of its appearance. The temperature falls with this resolution of the skin lesions. This syndrome suggests strongly an infectious disease of unknown etiology. We believe that this condition deserves to be considered a definite clinical entity.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CHASE — Lawrence M. Chase, M.D., of Carver, died February 8. He was in his sixty-first year.

Dr. Chase received his degree from Tufts College Medical School in 1904. He was a member of the Massachusetts Medical Society and the American Medical Association.

LANE — John W. Lane, M.D., of Dorchester, died December 3. He was in his sixty-seventh year.

Dr. Lane received his degree from Harvard Medical School in 1903. He was assistant demonstrator of anatomy at Tufts College Medical School from 1905 to 1908 and assistant in surgery, Courses for Graduates, Harvard Medical School, from 1912 to 1915. He served on the staffs of St. Margaret's, St. Elizabeth's and the Boston City hospitals. He was formerly a member of the Massachusetts Medical Society and the American Medical Association.

SULLIVAN — John T. Sullivan, Jr., M.D., of Boston, died December 10. He was in his seventy-first year.

Dr. Sullivan received his degree from Harvard Medical School in 1897. He was formerly school physician in Boston. He was a nose and throat specialist at the Carney and St. Elizabeth's hospitals and the Boston Sanatorium. He was a member of the Massachusetts Medical Society and the American Medical Association.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Haverhill	March 1	William T. Green
Lowell	March 3	Albert H. Brewster
Salem	March 6	Paul W. Hugenberger
Brockton	March 9	George W. Van Gorder
Springfield	March 15	Garry deN. Hough, Jr.
Worcester	March 17	John W. O'Meara
Pittsfield	March 20	Frank A. Slowick
Fall River	March 27	Eugene A. McCarthy
Hyannis	March 28	Paul L. Norton

WAR ACTIVITIES

INDUSTRIAL HYGIENE

Carbon Tetrachloride Poisoning in Parachute Factory

The cause of illness among 135 employees in a Kentucky plant manufacturing parachutes was traced to carbon tetrachloride used for cleaning soiled spots on the chutes, according to an investigation by the Kentucky Division of Industrial Hygiene. The outbreak of illness occurred during a period of ten days and was manifested by abdominal cramping, nausea and vomiting. Some workers complained of "bloating and difficulty in breathing." Many employees were acutely ill and unable to continue work. The illness lasted from two to five days in the average case, although a number of workers continued to feel bad after resuming work.

The possibilities of food poisoning were ruled out by questioning of ill employees about food consumed in the forty-eight hours preceding onset of illness. The absence of fever and diarrhea indicated that the disease was not an intestinal disorder of bacillary origin. On further study, the nursing records revealed that a great many employees complained of frequent or even constant headaches, and complaints of gastric distress had been especially numerous for several weeks. The fact that the incidence of the disease was restricted to workers on the first shift, and to those whose work placed them in the same environment, pointed to some special factor such as a toxic chemical. A check of the records revealed that out of 137 sick employees, 135 had been engaged in sewing and cleaning the nylon used in manufacture.

It was found that more cleaning of the chutes had been done in recent weeks and that at times pure carbon tetrachloride had been used in place of the usual solvent. The solvent was kept in open colltainers, and an estimated 4 gallons were used daily. With the beginning of the cold weather season five or six weeks previously, ventilation was provided only by opening windows along the skylight, the side windows being closed. Since the fumes of carbon tetrachloride gas have a density 5.3 times that of air, they could only be removed by vents at the floor level. It was significant that the first noted symptoms were coincidental with the beginning of heating, and the consequent reduction of ventilation in an effort to conserve fuel.

The recommendation made for substitution of some other solvent was quickly adopted. The use of carbon tetrachloride was immediately ordered discontinued, and cleaning of parachutes is now being done with soap and water. — Reprinted from *Industrial Hygiene News Letter* (January, 1944).

MISCELLANY

HEMORRHAGE IN PULMONARY TUBERCULOSIS

In the life of any individual the sudden spitting of blood is a dramatic and fear-stirring event. Usually it is brought to the attention of the physician so promptly that an accurate and rapid diagnosis is possible. Self-neglect, however, is encountered on the part of some patients. Errors in diagnosis, too, are not unheard-of happenings. Thus there is every good reason why such an alarming symptom as hemoptysis must be viewed with concern by the doctor until the cause has been established and the proper emergency care and long-term treatment provided. In this regard, the following abstract of a recent article (Minor, G. R. Hemorrhage in pulmonary tuberculosis. *Am. Rev. Tuberc.* 48:109-114, 1943) is of interest.

Pulmonary hemorrhage is one of the most distressing phenomena encountered in medical practice. The patient is gravely alarmed and the physician is confronted by bleeding that comes from a point deep within a delicate organ enclosed in a rigid framework. To combat the bleeding there may be only slowly or doubtfully effective physiologic mechanisms.

Psychologic effects to one side, hemoptysis generally is indicative of serious pulmonary disease. It is recognized that unexplained blood-spitting must be considered due to tuberculosis until proved otherwise. Occasional causes, however, include such nontuberculous diseases as bronchiectasis, bronchogenic carcinoma, lung abscess, rheumatic

heart disease and various minor nose and throat affections. People apparently in good health and presenting negative physical signs and few or equivocal roentgenologic findings represent especially puzzling problems when they report having coughed up blood. In all cases it is essential that we exhaust every means at our disposal of tracking down the reason for obscure lung hemorrhage.

The causes of hemoptysis are still not clearly understood. Blame has been laid on deficiency in one of the factors concerned in blood coagulation, on tonic, nervous or endocrine factors, on erosion of a vessel wall by a tuberculous process, on rupture of a small aneurysm within a cavity. Although the most serious hemorrhages occur in old, fibro-ulcerative tuberculosis, small or moderate hemoptyses may be seen in early disease, sometimes as the first recognizable symptom. Softening of a lesion or progression of an established process may be accompanied by hemorrhage.

Among 1000 patients consecutively discharged from the Blue Ridge Sanatorium, Charlottesville, Virginia, only those were included in this study who gave a clear-cut history of spitting up 1 dram or more of blood, or who suffered a hemorrhage during their stay in the institution. "Streaking," "streaked sputum" and indefinite history of hemoptysis were excluded. In all, 905 cases of tuberculosis, made up of 424 males and 481 females, included 220 who had hemoptyses during the active phase of the disease. This is an incidence of 24.3 per cent, regardless of the duration of observation.

Some of the largest hemorrhages in this series occurred in a few patients showing bronchiectasis or rheumatic heart disease. Bogen, including instances of streaks and clots, found that over half his patients with hemoptysis expectorated less than 2 ounces of blood. The present study records 106 cases with hemorrhages of stated amount, ranging from 1 dram to 2 quarts, the average being 5 ounces. This did not include repeated bleeding from the same individual on the same or subsequent days, since these were not thought to be distinct episodes, but more or less a continuation of the first. In approximately 40 per cent of the cases the episode of hemoptysis was repeated at least once.

Hemorrhage was the presenting symptom, often the initial evidence of trouble, in 60 cases. Perhaps nothing drives a patient to seek medical advice faster than the expectoration of a single mouthful of blood, although 23 patients did nothing about their initial hemorrhage.

When the local physician was consulted by persons with hemorrhage in cases of previously undiagnosed tuberculosis 70 per cent were properly diagnosed, and it is estimated that 84 per cent correct diagnoses could have been reached by further study.

Only 49 cases in the entire hemoptysis group failed to show a cavity on x-ray examination, and of these, 11 were found to be nontuberculous. No less than 83.4 per cent of the tuberculous cases with hemorrhage had a positive sputum. Of the 170 patients in this latter category, 159 had roentgenograms revealing consolidation, honeycombing, punching out or frank cavitation.

Correlation of hemoptysis with physical exertion, with direct chest trauma or with mechanical disturbance of the lung is possible in some cases, although hemorrhage may and often does appear when the patient is at rest, perhaps during sleep. In only 28 cases in this study was there either a specific history of a precipitating factor or of its absence. In 10 patients hemorrhage was related to one or more menstrual periods.

Among the graver consequences of pulmonary hemorrhage must be listed strangling and asphyxia from massive bleeding, fatal blood loss in the cachectic patient, and the commoner and ever-present danger that blood from a cavity that is generating a positive sputum will spread the infection to other parts of the lungs, giving rise to an acute tuberculous bronchopneumonia or a massive caseous pneumonia. Obviously, repeated episodes of blood-spitting multiply the chances for such complications to occur.

Summary and Conclusions

In a study of 1000 sanatorium tuberculous patients it was found that hemorrhages occurred in 24.3 per cent of them.

The average size of hemorrhage was 5 ounces. Forty per cent of hemorrhages were eventually repeated.

In 60 patients, the first remarkable symptom was hemoptysis.

Seventy per cent of cases with a history of hemorrhage before diagnosis were properly diagnosed by the local physician, when he was consulted. Thirteen per cent, however, were misdiagnosed.

Most tuberculous patients with hemorrhage have cavitation visible on x-ray examination; 83.4 per cent of this series had a positive sputum.

Trauma to the chest, strenuous exercise, mechanical disturbance of the lungs and, in females, the menstrual period are definite precipitating factors.

Small hemorrhages often occur from early lesions at the height of the catarrhal and toxemic symptoms that probably signify softening. These are not usually serious and may, in the long run, be beneficial if they call attention to an undiagnosed tuberculosis. The larger hemorrhages that occur in chronic ulcerative tuberculosis, however, although rarely immediately fatal, are accompanied by many unpleasant and dangerous possibilities. Of the 12 deaths that occurred in the sanatorium after hemoptysis, it is thought that 5 were directly or indirectly the result of the hemorrhage. — Reprinted, in part, from *Tuberculosis Abstracts* (January, 1944).

NOTE

Dr. Bennett F. Avery, dean of Boston University School of Medicine for the past three years, has recently been appointed director-general of public health of Iran. Since Dr. Avery was formerly a resident of the Near East, he is well fitted to assume this new responsibility. Although the date of his departure from the United States is indefinite, he has already severed his connections with the medical school.

CORRESPONDENCE

DYSENTERY

To the Editor: I was quite interested in the editorial "Dysentery" in the January 6 issue of the *Journal*.

I do not believe that under ordinary conditions the diarrheal diseases are sufficiently diagnosed to render their separation possible. Certainly only 1 or 2 per cent of the dysenteries in the military service are specifically diagnosed, and I doubt if the rate is any better in civil life. As expressed in a recent paper [Dysenteries and diarrheas. *War Med.* 4: 459-464, 1943], I do believe, however, that a practical differentiation of noninflammatory diarrhea from inflammations of the intestine can be made by a simple examination of the stool for exudate, and in many cases this examination will indicate the proper treatment before a therapeutic test is instituted.

I should also like to suggest that the use of emetine makes a much more satisfactory therapeutic test for amebic infection with symptoms than does that of either carbarsone or yatren, both of which require a considerable number of days before the therapeutic effect is evident.

Colonel Geo. R. Callender, M.C., U.S.A.
Army Medical Center
Washington, D. C.

NEED FOR MEDICAL AND SURGICAL SUPPLIES

To the Editor: There is a critical need for medical and surgical supplies that may lie hidden and forgotten in physicians' offices: discarded or tarnished instruments, surplus drugs, vitamins, infant foods and so forth. Collected, packaged and sent to the Medical and Surgical Relief Committee, they can play a vital role in its program of medical relief for the armed and civilian forces of the United Nations.

Surgical instruments and medicines are hungrily snatched by the medical corps of our allies. The work of war-zone hospitals and welfare agencies is too often crippled by the lack of medical supplies. Community nurseries in this country, and refugee camps abroad cry out for vitamins and baby foods for their ill-nourished charges.

The committee's roll call of medical requests — not one of which has been turned away — reads like a world geography: the Fighting French in North Africa and Tahiti; the Royal Norwegians in Canada and Iceland; the West Indies; South and Central Africa; China; India; Great Britain;

Yugoslavia; Greece; Syria; Russia; Alaska; and, of course, the United States.

To meet the demands that pour into headquarters, the committee needs all types of instruments, especially clamps, scalpels, forceps and all kinds of drugs, from iodine to sulfonamides. By contributing what they can spare, physicians will help speed another shipment of sorely needed medical aid.

JOSEPH PETER HOGUET, M.D., *Medical Director*
Medical and Surgical Relief Committee

420 Lexington Avenue
New York City

FLUORINE AND DENTAL HEALTH

To the Editor: In recent numbers of the *Journal* there have appeared a report of a committee of the Massachusetts Central Health Council, entitled "The Dental Needs of Massachusetts Children of Today," and also two editorials, one referring to this report and the other dealing with a council report, "Problems of Local Health Officers." It is a great satisfaction to find the *Journal* so willing to publish this important report, and to lend editorial comment to the fundamental work that the council is doing.

I doubt if all your readers know exactly what the Massachusetts Central Health Council is, even though the Massachusetts Medical Society is a member. It is composed of about a score of organizations, both official and nonofficial, that are carrying on work relating to public health on a statewide basis. These include the Massachusetts Department of Public Health, the Massachusetts Department of Labor and Industry, the Massachusetts Medical Society, the Massachusetts Public Health Association and similar agencies. It also includes as constituent agencies, city or town councils that themselves represent on the local level the same kind of "organization of organizations" formed for the purposes of cooperation, deliberation and collective action. Such organizations represent democracy at work in public health.

I want, especially, to make a brief comment on the report of the Dental Committee and the editorial thereon. As one concerned primarily with public health I have been greatly interested in the possibilities of the application of the recent work on fluorine and its relation to dental health as a community project. Here for the first time we seem to have a genuine prophylactic for dental caries that can be promoted as a public-health measure. The report itself devotes a short paragraph to this most important possibility, and the editorial does not even refer to it.

As in the case of cowpox virus, nature seems to have anticipated science, and the preventive phenomenon has been operating in certain communities for generations before being interpreted by McKay, Dean and others. It now seems well established that in amounts of one part per million and over, fluorine in drinking water reduces the prevalence of dental caries. In amounts appreciably above this it causes discoloration or dental fluorosis (so-called "mottled enamel"), with its accompanying disfiguring effects, but still showing a strikingly lowered incidence of caries. By analysis of the teeth of persons and of experimental animals it has been shown that fluorine in water or other articles of diet is metabolized, or in some manner incorporated into the tooth structure, presumably making the enamel more resistant to acid corrosion due to fermentation by *L. acidophilus*.

It also seems to be well established that the topical treatment of the teeth with fluorine compounds has a similar inhibitory action against caries. Therefore, private dentists and dental health clinics have at their disposal a true prophylactic that may be used for the benefit of the patient.

There remains the problem of whether fluorine in prophylactic amounts has any undetected deleterious effects of a cumulative nature, as well as the question of the control of dosage. Since a large number of people have for many years been exposed to public water supplies containing fluorine greatly in excess of the proposed prophylactic concentration, it should be possible to analyze the vital statistics of these populations and to examine the present physical state of health of these people in order to find the answer to the first question reasonably soon. The question of dosage in water seems relatively simple, since equipment similar to that now used for chlorine will serve. Even adjustment of dosage to meet the requirements of the relative water consumption at different times of year could be provided.

Fluorine in finely ground bone meal as a universal constituent of the diet has similar possibilities.

The topical treatment of the teeth with fluorine is strictly a dental practitioner's problem, which will surely be explored by that profession.

Of course, caution is indicated in any procedure that affects the general public health, and we must be as sure as we can be that a prophylactic measure will not boomerang. Nevertheless, there must be some venture in every new public-health or medical practice, and we must weigh the gains against the possible risks. Perhaps we have been more guilty of caution than daring in some cases — witness the lag in accepting pasteurization, for example.

I am confident that we have at last a weapon for the practice of public-health dentistry. We shall, in a few years, provide for the incorporation of fluorine in some universal article of diet, and local application of this chemical will become common. Let us be ready and not block this great beneficent discovery of a means of attacking man's most ubiquitous disease by any false prejudice or supercaution.

CURTIS MORRISON HILLIARD

Simmons College
Boston

RESULTS OF BOARD EXAMINATION IN NOVEMBER, 1943

To the Editor: Attached is a tabulation of the results of the examination given by the Board of Registration in Medicine on November 19, 1943, listed according to the medical school from which the applicants graduated.

H. QUIMBY GALLUPE, *Secretary*
Board of Registration in Medicine

State House
Boston

MEDICAL SCHOOL	No. PASSED	No. FAILED
Boston University School of Medicine	3	0
College of Physicians and Surgeons, Boston	0	18
Harvard Medical School	7	0
Tufts College Medical School	0	9
Massachusetts College of Osteopathy	60	83
Middlesex University	6	0
Chicago Medical School	7	2
Columbia University College of Physicians and Surgeons	2	0
Georgetown University	0	1
Jefferson Medical College	1	0
Johns Hopkins University School of Medicine	1	0
Kansas City University of Physicians and Surgeons	5	41
Kirksville College of Osteopathy and Surgery	0	3
Mid-West Medical College	0	6
Missouri College of Medicine and Science	0	1
Northwestern University	3	0
Ohio State University	2	0
Philadelphia College of Osteopathy	1	3
University of California	1	0
University of Maryland	1	0
University of Minnesota	2	0
University of Rochester	2	0
University of Berlin	0	1
University of Bologna	1	3
University of Breslau	0	1
University of Geneva	0	1
University of Hamburg	0	1
University of Heidelberg	1	1
University of Jena	1	1
University of Karl Franzens	1	0
University of Kariova	0	1
University of Kazan	0	1
University of Königsberg	0	1
University of Kola	1	0
University of Lausanne	0	2
University of Laval	0	1
University of Leipzig	0	1
University of Marseilles	1	0
University of Paris	2	0
University of Pisa	0	1
University of Prague	0	2
University of Regia	0	1
University of Tartu	0	1
University of Vienna	0	1
Totals	106	189

(*Notices on page xv*)